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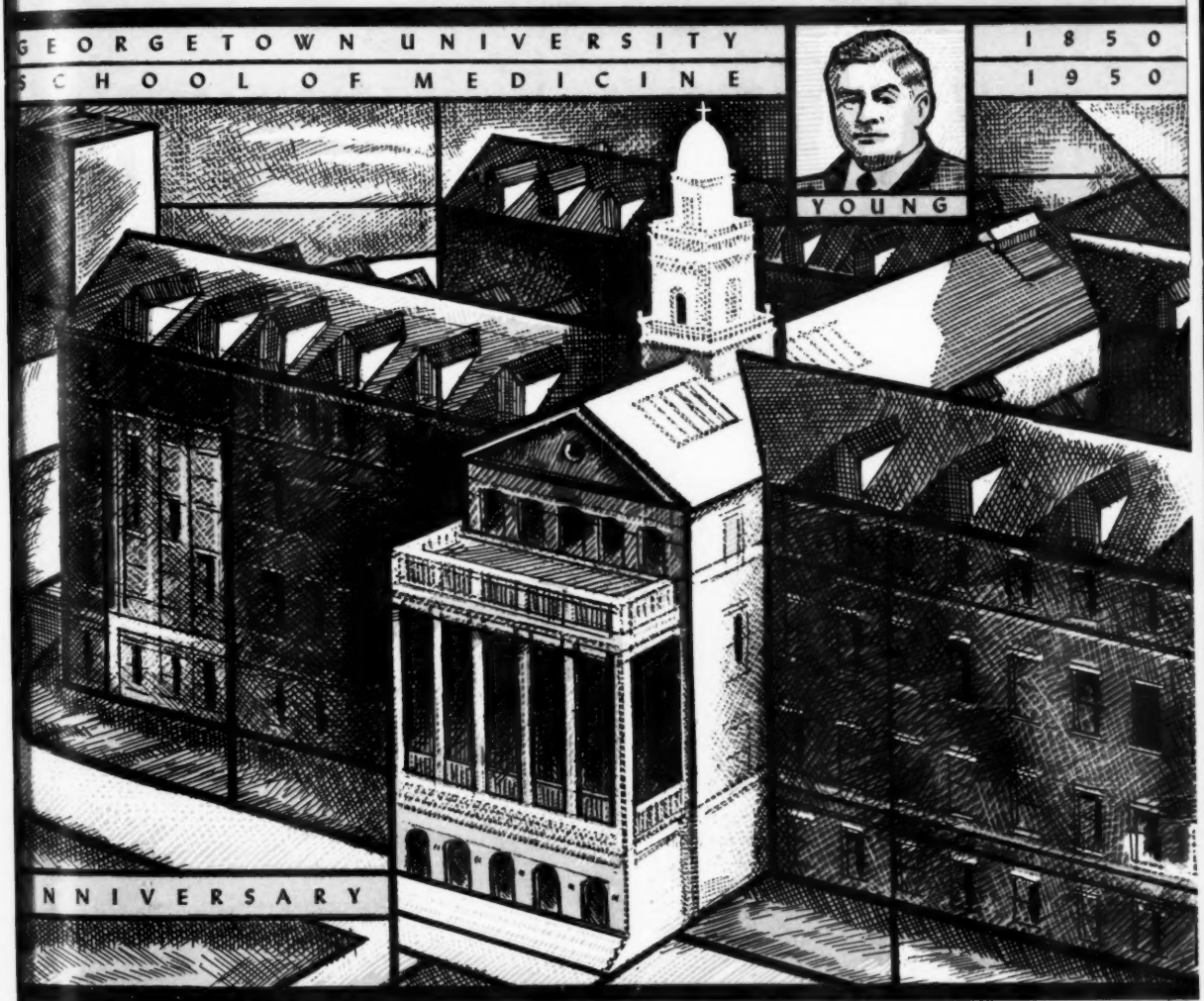

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. . . from Boston—the latest advances in

SPECIFIC METHODS of TREATMENT

See SAUNDERS Advertisement, Pages A-8 and A-9

CASE: 16*

54-year-old man suffers severe parkinsonism of seven years' duration. Symptoms unrelieved by scopolamine hydrobromide, but treatment with RABELLON *Compound of Belladonna Alkaloids provides marked benefit.*

G. T., a 54-year-old man, had been suffering from severe parkinsonism for seven years. For the last five years he had been taking 5.0 mg. of scopolamine hydrobromide daily.

Despite this therapy, severe symptoms of parkinsonism persisted. These included sialorrhea, hyperhidrosis, restlessness, depression, marked tremor and rigidity of the extremities, loss of associated movements, masked facies, slow gait and retropulsion.

Moreover, the patient was unable to write, button his clothing or wind his watch, and was frequently unable to eat without assistance. He had not worked for the last three years.

After examination by his present physician, it was decided to change treatment. For the next 20 days scopolamine hydrobromide was gradually withdrawn and replaced by smaller doses of RABELLON Tablets Compound of Belladonna Alkaloids, 4.0 mg. daily.

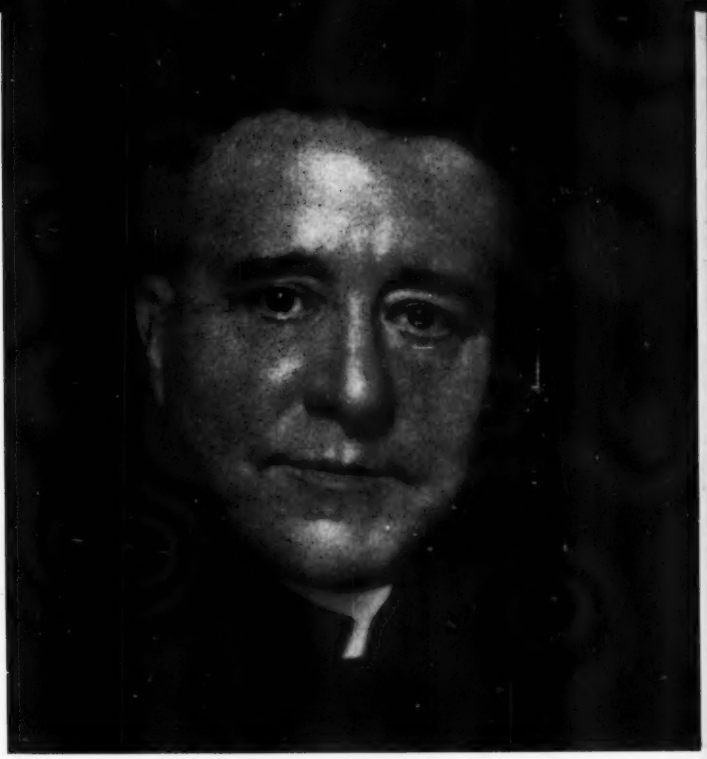
On this new therapy the patient's improvement was marked and rapid. He was soon able to eat without assistance, write, button his clothing, and wind his watch. Rigidity, muscle pain, hyperhidrosis, salivation and restlessness were greatly diminished. Gait, tremor and general spirits were much improved.

No toxic effects from RABELLON Tablets were experienced except for occasional slight dryness of mouth. The patient reported he felt "50 to 75 per cent better," and spoke of returning to his old job.

Note characteristic posture of hands and fingers, the "pill rolling" movement. Slightly flexed head and masklike features are characteristic of parkinsonism.

RABELLON® Tablets Compound of Belladonna Alkaloids afford prompt and marked symptomatic relief in most cases of parkinsonism and paralysis agitans. RABELLON Tablets contain definite, specific amounts of three purified belladonna alkaloids that have demonstrated their efficacy in fixed ratio. Supplied in bottles of 100 and 1,000 quarter-sected tablets. A generous sample for your clinical use will be sent on request from: *Professional Service Department, Sharp & Dohme, Box 7258, Philadelphia 1, Pa.*

*Actual case record



FOREWORD

PAUL A. MCNALLY, S.J.

It affords me great pleasure to be able to extend to the Editors of *Postgraduate Medicine* my very deepest thanks for their most gracious cooperation through the medium of their Journal in making the celebration of the 100th Anniversary of the founding of the Georgetown University School of Medicine the conspicuous occasion it should be to us and to all friends of medical learning.

I am sure the worthy editors of *Postgraduate Medicine* are, like ourselves, conscious of the invitation and challenge that is offered to all associated with the medical profession at this time when we are beginning the second hundred years of our existence. The rapid progress that has been made in all fields of medicine during the last several decades is indicative of the progress we may expect for the future. It is our intense hope here at Georgetown that being in the National Capital, we may be intimately associated with each forward movement that may be made. Certainly if the enthusiastic encouragement connected with our 100th Anniversary Celebration is an indication of the cooperation we may anticipate, then we may look forward to the Georgetown University School of Medicine participating in the great contributions to the well-being of mankind that are certain to be made in the years ahead.

In closing, may I express again in my own name, in the name of the Medical School, and in the name of the entire University, our deep appreciation of the gracious contribution of the Editors of *Postgraduate Medicine* in making the celebration of our 100th Anniversary an outstanding event.

Paul A. McNally, S.J.

DEAN

Progress in Anesthesiology

EDWARD B. TUOHY*

GEORGETOWN UNIVERSITY MEDICAL CENTER, WASHINGTON, D. C.

It is easier to relate the background of this specialty than it is to keep pace with newer concepts and developments in anesthesiology. Certain fundamental considerations have served as the foundation for many of the practices in anesthesia today.

To mention but a few of the fundamentals we must recall that toxicity studies of various agents were absolutely necessary, and that ether has withstood the test of more than one hundred years of comparatively safe use. Improvement in methods of administration of ether as well as of other agents has been significant. The intratracheal method of Magill[1] unquestionably has been one of the most important advances in the last twenty-five years. This principle has emphasized the established fact that a patent unobstructed airway is a necessity with inhalation and intravenous anesthesia, or in fact with any type of general anesthesia.

Carbon dioxide absorption with the closed or semi-closed method of inhalation anesthesia was suggested by Jackson[2] and popularized and improved by Waters.[3] This principle of carbon dioxide absorption has been a definite economic asset as well as the more important physiologic contribution. It permits the use of agents which would be quite prohibitive in cost if circle or to-and-fro respiration with carbon dioxide absorption were not available.

More recently, intravenous anesthesia, originally limited to barbiturates of the longer-acting variety such as nembutal and sodium amytal, has made a definite niche in our concept of methods of anesthesia. It has stimulated investigation with many agents, and currently there can be no doubt about the utility and safety of thiopental.

*Professor of Anesthesiology, Georgetown University Medical Center, Washington, D. C.

INFLUENCE OF INTRAVENOUS ANESTHESIA

The almost universal acceptance of intravenous anesthesia, particularly with thiopental, was due in a large measure to experience originally reported by Lundy[4] and associates, and then later by the tremendous use of it in the late war. This agent was employed more than any other single agent or combination of agents.

The advantages of thiopental have been well established, and the text on intravenous anesthesia by Adams[5] clearly outlines the basic considerations and safety measures for this type of anesthesia. Quite naturally, however, with an agent as adaptable and apparently safe for many operations, certain pitfalls became obvious. Those individuals who had a vast experience with this agent were aware of some of the shortcomings of thiopental, such as respiratory depression especially in very young and elderly patients, and the lack of profound muscular relaxation.

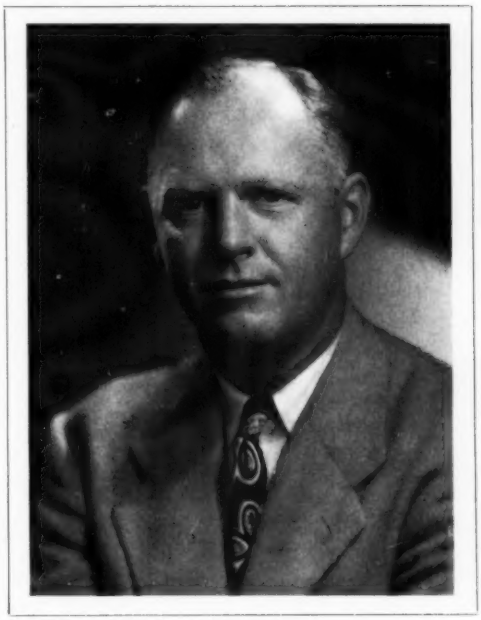
If an intravenous anesthetic agent could be found which provided smooth induction and recovery, good muscular relaxation, and minimal toxicity, there could be little more to be desired. The inability of thiopental to produce excellent relaxation of muscles in all instances became apparent, and efforts were made to find new agents or to augment an agent such as thiopental to obtain the desired muscle relaxant effect.

Curare is the agent first suggested to en-

hance the action of intravenous anesthesia. This agent or its active principle, d-tubocurarine chloride, proved to be most helpful with thiopental. The ability to produce muscle relaxation supplied the "missing link," so to speak, in the safe administration of thiopental. With careful technic of administration serious central barbiturate depression of respiration could be avoided. Curare would provide the relaxation and thiopental the anesthesia. For the most part these two agents can be used for almost any operation, but trouble can be encountered with this technic, and I might add quite rapidly. In other words, respiratory depression or apnea can occur, and when it does, immediate steps must be taken to provide assisted pulmonary ventilation. Briefly, this means that all of the basic facilities for artificial respiration must be available at all times.

In addition to curare certain other muscle relaxants are available. They are decamethonium bromide (C_{10}), flaccidil, myanesin, and others. They possess a pharmacologic action similar to curare. Allegedly, C_{10} does have some advantages over curare. There appears to be less tendency to bronchospasm when this agent is used with thiopental.

With such agents as curare it has been expedient to search out certain antagonists of a pharmacologic nature. Prostigmine is reasonably effective to counteract curare, and more recently a prostigmine analogue (RO 2-2561),* yet unnamed, has evidence which indicates that this agent is quite active in reversing the action of curare. By way of summation with respect to curare and muscle relaxants of different genesis it is reasonable to state that these agents have augmented materially our use of intravenous anesthesia.



EDWARD B. TUOHY

NEWER INTRAVENOUS ANESTHETICS

Surital sodium, 5-allyl-5 (1-methylbutyl)-2-thiobarbituric acid, has been introduced within the last year or so, and it is very similar in action to thiopental.[6] Were it not for the fact that thiopental has had such a wide use and variable application, it is my opinion that surital sodium would be equally effective. Suffice it to say that surital sodium in its clinical application has two rather distinct differences from thiopental, namely, a more rapid induction period in equivalent concentration and a slightly higher incidence of postoperative nausea. Other than these considerations we have employed surital in a relatively small number of cases and perhaps it is not wise therefore to proffer any prediction. A thousand cases would not be anywhere near sufficient to offer a true comparison with thiopental. Surital sodium is compatible with most muscle relaxant agents, and the end result closely approaches that of curare and thiopental or thiopental and C_{10}.

A new spirothiobarbiturate has been introduced recently and it has certain significant characteristics, such as a smooth induction and rapid or ultra-rapid recovery. The degree of analgesia and motor relaxation does not appear to equal that of thiopental or surital sodium. However, when these qualifications are not needed the spirothiobarbiturate has an application. The rapid recovery period is significant.

ADVANCES IN ANESTHETIC MANAGEMENT

The overall conduct of safe and adequate anesthesia combines the careful selection of premedication, the judicious combination of anesthetic agents and methods, the replacement of fluids including blood, glucose, saline, and other

*Hoffmann-LaRoche, Inc.

basic components of adequate electrolyte therapy. The advances to be made quite naturally follow along these lines, but in addition progress into more fundamental considerations of basal physiologic tolerance to anesthetic agents and other adjuvants.

Faulconer[7] has contributed brilliantly to a more profound understanding of the events incident to anesthetic administration. His work has shown not only the relative quantitative inadequacies of inhalation anesthesia with respect to concentrations of oxygen and anesthetic vapors and gases, but has provided by means of a most ingenious apparatus a method whereby anesthesia conduct can be intimately correlated, not to mention control. He has combined his own apparatus which briefly analyzes gas, ether, and oxygen concentrations at any given instant with the intricacies of the electroencephalograph.

Currently, many surgical anesthetics can be controlled automatically, so to speak, by a direct relay activation incident to substantial alterations in the electrical components affiliated with brain activity. This contribution and basic improvement in technic has and will enhance our ultimate conduct of anesthesia. Evidence is at hand already which indicates that so-called surgical shock may be prognosticated much earlier than heretofore, and that the usual premonitory signs assigned to incipient shock may be in substance late or later signs. It behooves all anesthesiologists to consider this contribution and to utilize methods which will eliminate insofar as possible some of the "guess work" from anesthesia. Granted the fact that experience is vital, but let it be said also that human skill and observation need finite aid in accomplishing the best that is possible in anesthesia management.

Assistance available from recent pharmacophysiologic research has been invaluable to anesthesia. The gamut of sympathetic and parasympathetic stimulating and "blocking" agents is amazing. In fact these new facts with respect to the autonomic nervous system are essential to progressive anesthesia, and in certain instances, such as the management of adrenal or other chromaffin tissue tumors (pheochromocytoma), certain agents and concepts are a necessity. In passing, a few of these "blocking" agents should be mentioned at least by name and their application studied clinically. T.E.P. (tetra-ethyl pyrophosphate), D.F.P. (diiso propyl fluro phosphate), dibenamine, priscol, etc., are but a few examples.

Anesthesiology in a relatively short time has established a firm base for the development of a solid structure which can be integrated into many branches of medicine. Many medical and diagnostic problems may be assisted by anesthetic technic. Examples of such aid are: treatment of neurovascular diseases by means of sympathetic nerve block, including cerebrovascular thrombosis or embolus. Likewise, the whole problem of pain relief has been more and more the interest and concern of the anesthesiologist. Oxygen therapy, blood transfusion, and fluid therapy are also intimate problems with anesthesia.

It has been the singular aim of anesthesiology to provide safe analgesia and anesthesia for the patient before, during, and after surgery. Postanesthetic recovery or observation rooms have been a substantial contribution to safer surgery. Patients are watched diligently during their recovery from anesthesia and any supportive therapy is readily available. Furthermore, these rooms materially economize on personnel.

The fields of geriatric and pediatric medicine, which have been brought forward so rapidly, have been enhanced by anesthesiology. New agents and improved technics have made surgery more flexible in these two extremes of age. Leigh[8] has made very notable contributions in pediatric anesthesia. Of special importance is his respiratory valve for intratracheal anesthesia and premedication technics for children. Regional anesthesia with careful combinations of intravenous anesthesia is well adapted to geriatric surgery.

It has been shown that intravenous alcohol is quite useful in parenteral therapy.[9] It provides calories and has definite analgesic properties. Alcohol in 5 to 7.5 per cent concentration combined with amino acids is a fine mixture for intravenous feeding. The amount of morphine or morphine substitute can be reduced by administering alcohol intravenously. The reduction may be as much as 50 to 70 per cent. Continuous intravenous therapy has been simplified by the use of plastic tubing which can be slipped into the vein (via a needle) and left in situ for several days. This technic allows the patient to move the extremity, if so desired, while the fluid is administered. Complications (thrombosis) are minimal. Larger plastic tubing is available for blood transfusion, if desired.

COMMENT

Perhaps the most significant progress that has been made in the last ten years is the appreciation of teamwork between surgery and anesthesiology. The late war showed very clearly the value of physicians well trained in anesthesia. In fact, the specialty has oversold itself somewhat and there is more demand than there is available personnel. This situation will change gradually and will improve as more physicians are trained in the specialty. There are multiple opportunities in the field of anesthesiology for young men with sound training. In progressive medical teaching anesthesiology commands a significant and important role. Equality with other specialties is recognized and the ancillary attitudes previously ascribed to it are fading.

It has been said that good surgery deserves good anesthesia and that poor or mediocre surgery requires it. Surgery today is becoming quite bold, and at the moment surgery on the heart is one of our greatest challenges. The brilliant research work in cardiac physiology has made possible some of the more dramatic surgical attacks on the heart. Anesthesia has been important also along with the closest cooperation of the surgeon. More and more it is evident that the patient-surgeon-anesthesiologist relationship is very closely integrated, and continued progress with significant achievement and individual consideration will follow only if this harmony is maintained.

The art of anesthesia, like the inherited gift of intelligence, varies, but devotion to principles of science, ethics, and medicine is an opportunity which should never change.

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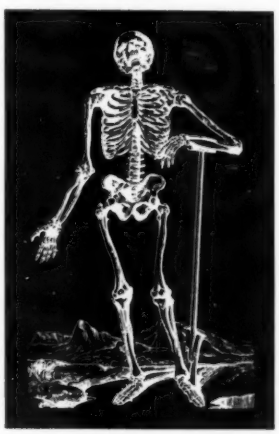


The Hypersensitive Carotid Sinus

J. ROSS VEAL[1] AND RICHARD BAUERSFELD

GEORGETOWN UNIVERSITY SCHOOL OF MEDICINE, WASHINGTON, D. C.

One of the most dramatic experiences encountered by man is that of suddenly losing consciousness. There are many causes of syncope, but none that upsets the cardiovascular system so quickly and profoundly as that which follows stimulation of the hypersensitive carotid sinus. When a patient suddenly "blacks out" from turning his head to one side, or simply by pressing on the side of his neck, he is greatly disturbed. Apprehension is so marked that these patients live in fear each day. Once they have lived through the experience, they dread its recurrence.

The unraveling of the mechanism of the syncope that follows stimulation of the carotid sinus has been a triumph in physiologic research. The recognition of the pathologic syndrome caused by the hypersensitive carotid sinus reflex has cleared up the mystery of one form of syncope. The discovery that the "blackouts" can be prevented through the elimination of this reflex by surgery, without producing ill effects on the patient, completes the cycle of achievement in conquering one of man's ills.

The first portion of each internal carotid artery presents a bulbous dilatation and this forms the carotid sinus. It may extend into the upper portion of the common carotid. The wall of the sinus is richly supplied by sensory receptor nerves which terminate in menisci, located largely in the adventitia. These emerge from the sinus as the sinus nerve (nerve of Hering) and ascend between the internal and external carotids to join the glossopharyngeal. It also receives a small branch from the carotid body and sends small filaments to the vagus and superior cervical ganglion.[1] Centrally, the fibers end in the vasomotor and cardioinhibitory centers in the medulla. The centrifugal part of the reflex arc is through the vagus (for the heart) and the sympathetic (for the blood vessels). It is the variation in the peripheral distribution that differentiates the type of symptoms produced.

The carotid sinuses, along with the aortic nerves, serve as an important reflex regulatory mechanism in the blood pressure;[2] they also influence the vagal and cardioinhibitory centers. Under certain conditions these nerve centers may become so hypersensitive to ordinary stimuli that an alarming circulatory collapse and syncope may follow.

The carotid sinus reflex presents a very complex mechanism. Impulses from the sinus may produce a rise or fall in the blood pressure; they may produce a slowing of the heart rate, or may increase it; they may cause vasoconstriction or vasodilatation; they may stimulate or depress the respiration. The carotid sinus, therefore, mediates both pressor and depressor effects on the circulation.[3]

H. E. Herring in 1923[4] originally described the mechanism of the carotid sinus reflex and following his description many investigators have contributed to the elucidation of the reflex.

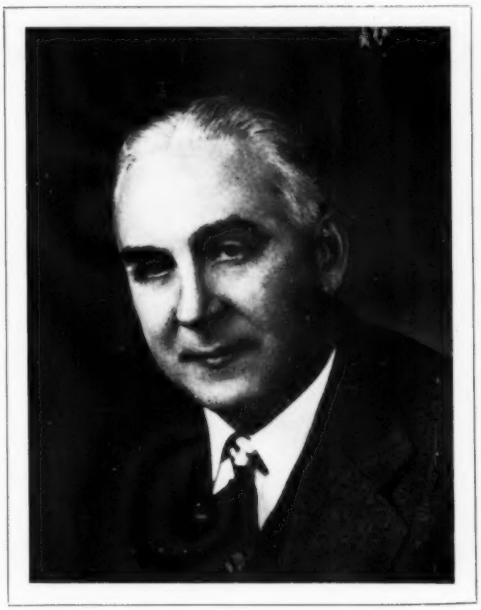
[1]Associate Professor of Surgery.

From Georgetown University Medical School and Cardiovascular and Vascular Surgical Departments, Emergency Hospital, Washington, D. C.

EXCITATION of the carotid sinus reflex is produced mainly through changes in pressure within the carotid sinus itself. A rise in pressure causes a slowing of the heart rate, a fall in blood pressure, general vasodilatation, a decreased secretion of epinephrine, and slowing of respiration.[2,5-7] If the pressure within the carotid sinus is decreased, reflex stimuli from the sinus will cause a rise in blood pressure, an increased heart rate, vasoconstriction, an increased secretion of epinephrine, and an increase in respiration.[2,5-7] These are natural phenomena which are directed towards the maintenance of a stable circulation. When the systemic arterial pressure is increased, the depressor effects predominate and when the systemic pressure is decreased, the pressor effects predominate.

Bronk and Stella[8] showed that there is a rhythmic discharge of nervous impulses over the sinus nerves and that the rate of discharge is directly proportional to the pressure in the carotid sinus. Increasing pressure in the carotid sinus will increase the frequency of these impulses with a consequent slowing of the heart and vasodilatation. It has been shown by oscillographic studies that during a depressor reflex efferent impulses discharging over the cardiac accelerator and vasoconstrictor nerves are reduced in frequency and may even cease. Reduction in the tension upon the vascular wall, by lessening the intensity of the stimulus to the nerve endings, lowers the frequency of the impulse formation and lessens the tonic depressor effect so that a rise in blood pressure results. "Thus, as the pressure within the sinus rises the frequency of the action currents of the sinus nerve increases. As many more impulses per unit of time arrive at the brain-stem centers, the same effects are produced that may be obtained from increasing the frequency of artificial stimulation of the sinus nerve itself. When sinus pressure is lowered the reverse effects are obtained."[3]

This reflex control of the circulation is so finely adjusted that we are hardly aware of its function. When the sinus becomes abnormally hypersensitive, ordinary stimuli may produce circulatory changes which are truly pathologic. Just how abnormal hypersensitivity develops is not clearly understood. It is known that dilatation of the carotid artery, including the internal carotid branch, may induce hypersensitivity. Certain changes in the vessel wall, as arteriosclerosis, pressure from tumors, or enlarged lymph glands, in the region of the sinus may effect an increase in its sensitivity.



J. ROSS VEAL

Rovenstine[9] and Ruzicku[10] have shown that certain drugs may sensitize the carotid sinus. Among such drugs are the volatile anesthetics, digitalis, and barbiturates. When the carotid sinus becomes hypersensitive the reflex mechanism loses its fine adjustment. The effect of stimuli is the production of an exaggerated reflex, which may result in circulatory collapse.

The patient with a hypersensitive carotid sinus reflex may present milder manifestations of vasomotor instability, such as palpitation, moist palms, emotional instability, low metabolism, and various neurogenic skin lesions.[3,5,7]

The various clinical manifestations of a hypersensitive carotid sinus reflex have been thoroughly studied by Weiss and his co-workers.[5-7,11] On the basis of their studies, Weiss divided the reactions into three types. The first, or vagal type (Figure 1a) is due to reflex vagal inhibition of the heart with a resultant fall in blood pressure, dependent upon the cardiac slowing. The efferent pathway in this type is through the vagus nerve.

In Figure 1a the pathway of the stimuli from the hypersensitive carotid sinus in the vagal type is represented. Stimuli pass over the sinus

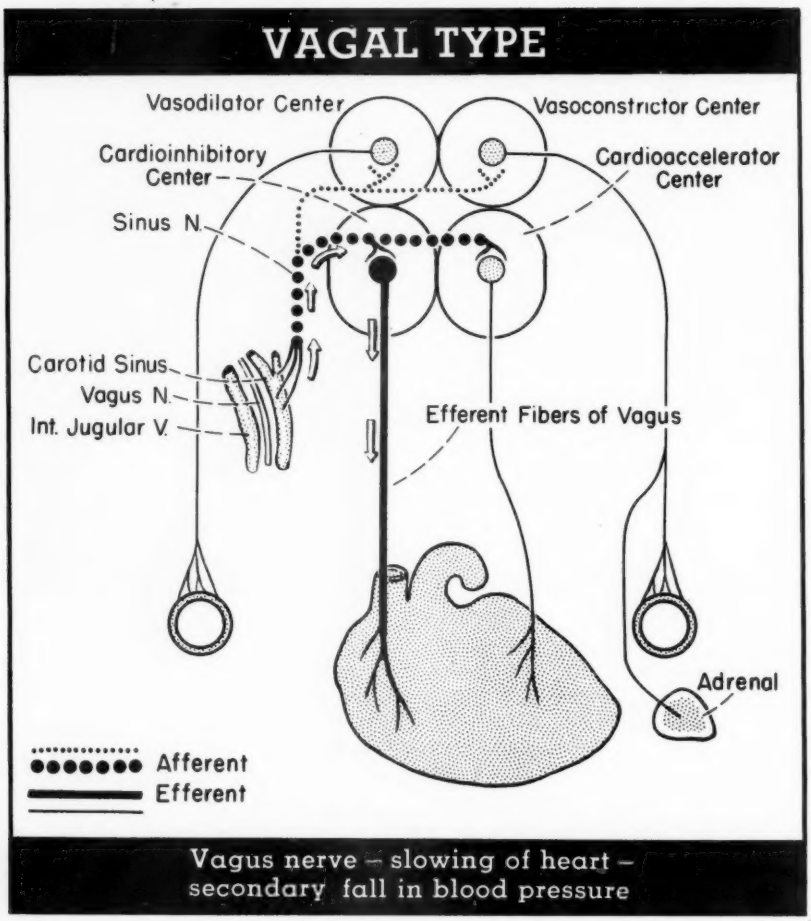


FIGURE 1a. A diagrammatic representation of the reflex arch in the vagal type. The stimuli ascend along the sinus nerve to the vasomotor and cardioinhibitory centers in the brain. Although both centers are affected the main effect is on the vagus nerve. The impulses then travel down the vagi to the heart resulting in cardiac slowing.

nerve to the vasomotor and cardioinhibitory centers and then centrifugally via the vagus to the heart and via the sympathetics to the blood vessels. The main effect is through the vagus and the result is a decreased heart rate. This effect is shown in the electrocardiogram in Figures 3 and 6. The vagal type is the most common and fortunately is the one most easily recognized.

In the second or depressor type of reaction (Figure 1b) the efferent arm is the aortic depressor nerve. In this type the clinical signs are due to cerebral anoxemia resulting from vasodilatation and a secondary fall in blood pressure, entirely unrelated to cardiac slowing or any arrhythmia. The important point is the "rate of change from the normal to the ischemic state rather than the absolute degree of cerebral ischemia."[3] The pathways of the stimuli from the carotid sinus to the vasomotor and cardioinhibitory centers in this type are shown in Figure 1b. Note that the main effect is on the vasomotor centers. The vagus is not primarily involved. The efferent arm of the reflex

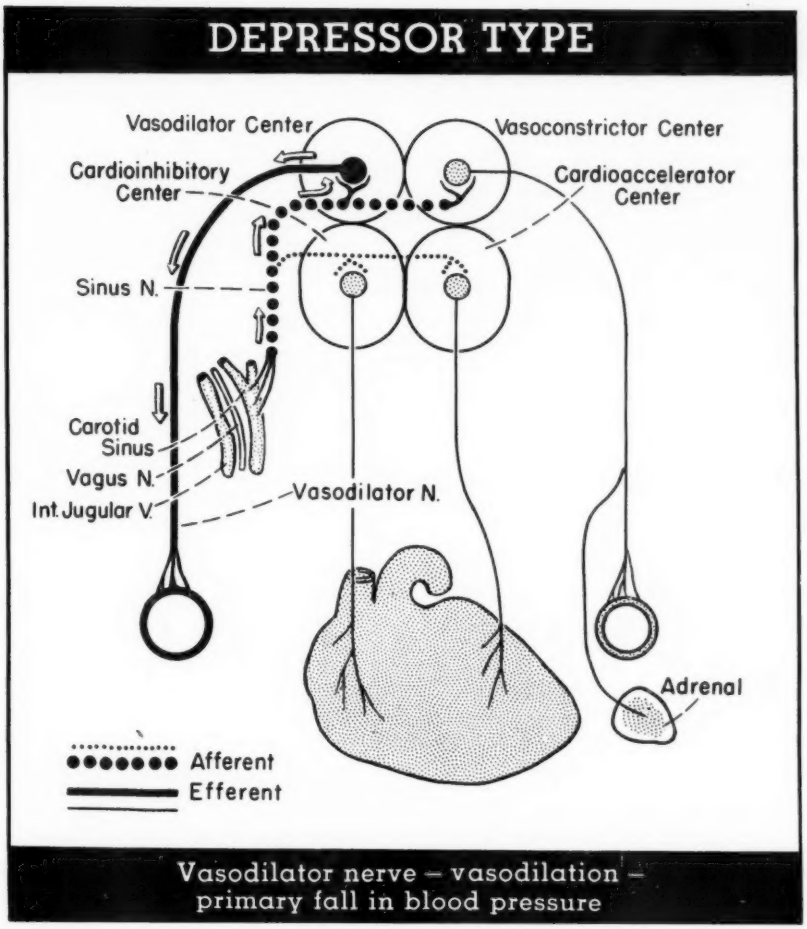


FIGURE 1b. A diagrammatic representation of the reflex arch in the depressor type of reaction. In this case the stimuli ascend along the sinus nerve to the brain-stem centers affecting mainly the vasodilator center. The impulses then pass centrifugally via the vasodilator nerve to the blood vessels resulting in vasodilatation and a fall in blood pressure.

is through the vasodilator nerve, resulting in vasodilatation and a fall in blood pressure.

In the third or cerebral type there is neither a fall in blood pressure or heart rate[12, 13] and the total blood flow to the brain is normal,[6] so that the symptoms cannot be attributed to changes in the cerebral flow. The efferent impulses arise in the carotid sinus and travel to the medulla and from there to certain vegetative centers in the region of the hypothalamus, the function of which is the regulation of consciousness; or to the blood vessels which supply such areas. This is the least common of the three types.

Spontaneous attacks of unconsciousness due to a hypersensitive carotid sinus reflex may be precipitated in many ways, such as sudden turning of the head, extending the arms over the head, wearing a tight collar, lying on the sensitive side, or a blow over the sinus. Sudden emotional disturbance may precipitate an attack.[3, 14] The attacks vary [5-7, 15] both in intensity and frequency. They almost always occur spontaneously while the patient is in the upright position, rarely in other positions. The spon-

NORMAL PREOPERATIVE TRACING

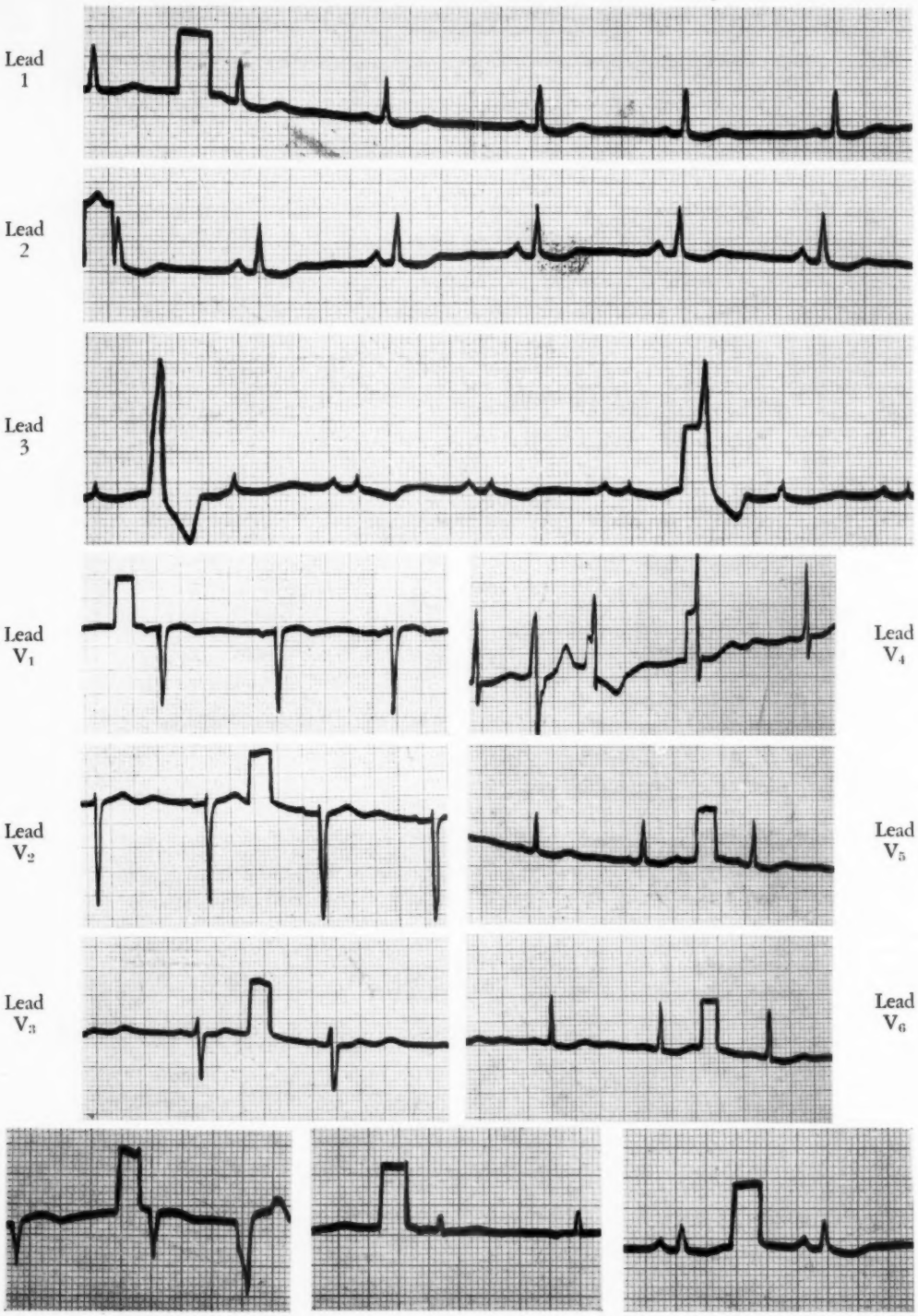


FIGURE 2. Tracing within normal limits except for frequent ventricular premature contractions.

PREOPERATIVE TRACING WITH CAROTID SINUS PRESSURE

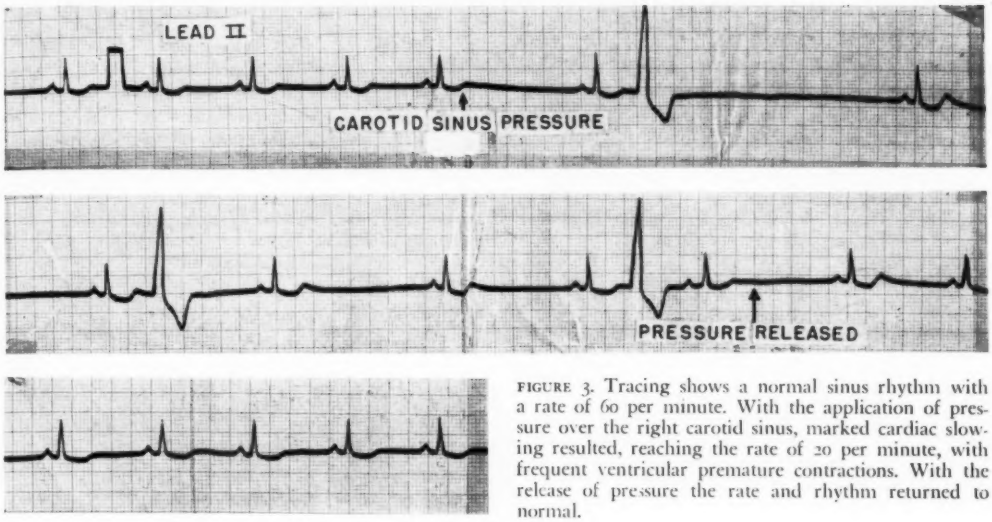


FIGURE 3. Tracing shows a normal sinus rhythm with a rate of 60 per minute. With the application of pressure over the right carotid sinus, marked cardiac slowing resulted, reaching the rate of 20 per minute, with frequent ventricular premature contractions. With the release of pressure the rate and rhythm returned to normal.

POSTOPERATIVE TRACING WITH CAROTID SINUS PRESSURE

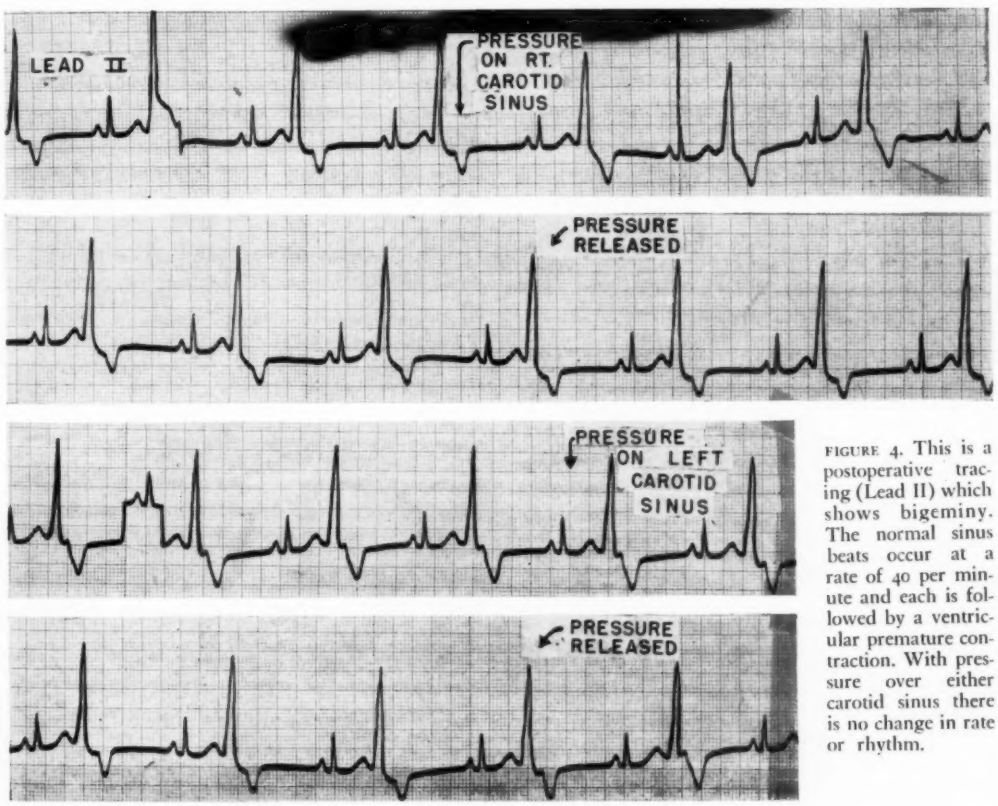


FIGURE 4. This is a postoperative tracing (Lead II) which shows bigeminy. The normal sinus beats occur at a rate of 40 per minute and each is followed by a ventricular premature contraction. With pressure over either carotid sinus there is no change in rate or rhythm.

taneous attacks last only from one to three minutes and are characterized by an aura[6,7,14] during which the patient may experience dizziness, weakness, epigastric distress, and ringing in the ears. This is followed by a period of unconsciousness, often associated with a convulsion which usually begins in the contralateral extremities and then becomes generalized. A pallor of the face usually precedes the period of unconsciousness. Biting of the tongue and incontinence of urine rarely occur. Recovery is usually prompt[15] and complete except for an occasional headache or dizziness. If the attacks are repeated at short intervals certain grave complications may follow. In one of our cases (case 3) serious neurologic disturbances resulted, apparently from thrombosis of small cerebral vessels during the period in which there was circulatory depression.

We have not seen any permanent damage to the heart as a result of a hypersensitive carotid sinus. However, electrocardiograms[7,14,16] taken during periods of induced syncope may show certain temporary abnormalities. The main changes are those of interference with the impulse formation in the S-A node and its propagation along the auricles and conducting apparatus (Figures 3 and 6). The stimuli are mediated through the vagus whose terminals are found in both the S-A and A-V nodes. The principal electrocardiographic finding has been a slowing of the heart due to varying degrees of A-V block. Cardiac asystole may occur.[14] Occasionally changes in the auricular complex, ventricular premature contractions, and ventricular escape may occur. Changes in the R-wave and St-T are rare.

This condition, hypersensitive carotid sinus reflex, is not frequently seen in large general hospitals. Undoubtedly, some cases are not diagnosed simply because the examining physician is not familiar with the symptom complex. We have seen cases that had remained undiagnosed for several years, although they had presented themselves for medical attention. In one case the patient was discharged from the hospital without a diagnosis after being "thoroughly" studied. He was seen by an astute physician as he was leaving the ward and again related his symptoms. The physician applied pressure to his right carotid sinus and the patient immediately collapsed at his feet. Any patient presenting a history of syncopal attacks deserves a thorough study to rule out a hypersensitive carotid sinus.

The diagnosis of a hypersensitive carotid sinus reflex is easily determined. The attacks of syncope usually can be induced by applying digital pressure over the carotid sinus. It may be further differentiated from other types of syncope by blocking the sinus with novocain. When the nerve pathways are blocked local digital pressure will no longer induce an attack.

We would like to present 4 case histories of hypersensitive carotid sinus reflex to emphasize certain points in diagnosis, etiology, and possible sequelae of frequent episodes of syncope. The first case is that of the common vagal type in which abnormal dilatation of the upper carotid, external carotid, and internal carotid arteries was present.

CASE REPORTS

Case 1—R. B., a 52-year-old Negro female. In 1942 she first experienced sharp substernal pains which did not radiate and were not associated with dyspnea or sweating. She was seen by a private physician, who advised a period of bed rest for three weeks; during this time she took digitalis, but has taken none since. She did well until 1944 when she experienced an episode of fainting unassociated with pain or dyspnea. Since then she has had recurrent episodes of fainting, about one every one to two months. These have been precipitated by suddenly looking upward, turning suddenly, or by reaching above her head. These attacks have not been preceded by an aura but are followed by headaches. The patient was admitted on February 9, 1950, for an evaluation of her fainting episodes.

Physical examination revealed a well developed but undernourished Negro female who did not appear acutely ill. Her temperature was 98.6° F., pulse 92, blood pressure 160/100. Examination of the neck revealed a distinct dilatation of the right common carotid artery at the point of its bifurcation. Slight digital pressure over this region produced a typical hypersensitive carotid sinus reflex attack. The left side was normal and showed no reaction to pressure. The rest of the physical examination was essentially negative. The electrocardiogram was normal (Figure 2). Electrocardiograms (Figure 3) taken during a period of induced syncope revealed marked cardiac slowing. On February 21, 1950, the right carotid sinus was denervated and the patient made an uneventful recovery. Follow-up studies show that she has not experienced any more periods of syncope and it has been impossible to produce an attack by pressure over the carotid sinus (Figure 4).

The second case presented attacks of syncope which followed the enlargement of lymph glands in the region of the right carotid sinus.

Case 2—R. T., a 32-year-old Negro male. Two weeks prior to admission, while driving his car, the patient

suddenly broke out in a cold sweat, became nauseated, and fainted. He was seen at a local hospital and after several hours was sent home without any medication or instructions. Apparently the significance of his complaint was not recognized.

In 1936 he had had a tonsillectomy and following surgery developed some enlarged lymph glands on the right side. About two weeks after surgery he developed a sore throat and these glands became larger and tender. While rubbing them he suddenly fainted. Since that time he has had frequent episodes of sudden dizziness and weakness which usually occur when looking up while at work as a paperhanger. He has also had attacks while shaving and they are more pronounced whenever he has a sore throat. Their frequency has always increased during the periods of an upper respiratory infection.

His past history revealed appendectomy, tonsillectomy, and in 1942 he was rejected by the draft because of hypertension.

Physical examination revealed a well developed and well nourished Negro male who did not appear ill. Temperature was 98.8° F., respiration 14, pulse 70, blood pressure 150/90. There were no abnormal findings, except for the neck. On the right side there was a firm, discrete, nontender lymph node which was freely movable. Slight pressure on this node produced the symptoms of weakness and dizziness, with a resultant slowing of the heart rate (Figures 5 and 6). Moderate pressure produced syncope which would last about 20 seconds and was followed by a feeling of weakness and headache. A denervation of the carotid sinus has been advised.

The third case presented a progressive cerebral deterioration following the first syncopal attack. This attack occurred while he was working as a plumber and was apparently initiated by extreme extension of his head.

Case 3—G. O., a 63-year-old white male, entered the hospital on May 1, 1950, after having suddenly fainted while at work. The patient was working as a plumber when he suddenly fainted and fell, fracturing a rib on the right side. He was hospitalized and studied but no definite diagnosis was made. Since discharge he has had several episodes of dizziness but no actual fainting. These attacks have always been associated with sudden change in position. During the next month he noticed a progressive motor aphasia and eighth nerve deafness. On closer examination it was found that slight pressure over either carotid sinus would produce asystole, although the right side appeared to be more sensitive. The patient was readmitted on June 7, 1950. Examination at this time revealed a marked motor aphasia, eighth nerve deafness, and a bilaterally sensitive carotid sinus. The rest of the physical examination was negative. The attending physician plans to give this patient a trial with large doses of atropine and if this is unsuccessful a denervation will be done.

The fourth case presented the common unilateral (right) vagal type. He was relieved by denervation of the involved side. Several months later, however, his "blackout" episodes recurred and on examination it was found that the left carotid sinus had become hypersensitive. He was cured when the left side was denervated. Bilateral denervation has not produced any untoward effects in this patient.

Case 4—F. W., a 51-year-old white male taxicab driver, was admitted to Gallinger Hospital on March 12, 1942. For two years he had experienced short bouts of dizziness and blurring of vision. One day while receiving a fare he turned his head sharply to the right and promptly collapsed. He fell upon the seat in an unconscious state. Within a few minutes he regained consciousness but felt extremely tired and was unable to focus. He was admitted to a local hospital for treatment. Although he had several attacks of syncope during his hospital stay, their cause was not determined. He was discharged and on leaving the ward stopped and related his history to a passing physician. This physician applied pressure over the right carotid sinus and the patient collapsed. He was later sent to Gallinger Hospital for denervation of the right carotid sinus.

On admission his blood pressure was 124/84. His temperature, pulse, and respirations were normal. Syncope could be readily induced by digital pressure over the right sinus but pressure over the left did not produce any reaction. The syncopal attacks were associated with marked slowing of the heart rate, rapid decline in blood pressure, and increase in respiration. The right carotid sinus was denervated under local anesthesia on March 17, 1942. Following this procedure the attacks could no longer be produced by pressure over the carotid sinuses. The general condition was good and he was discharged as cured.

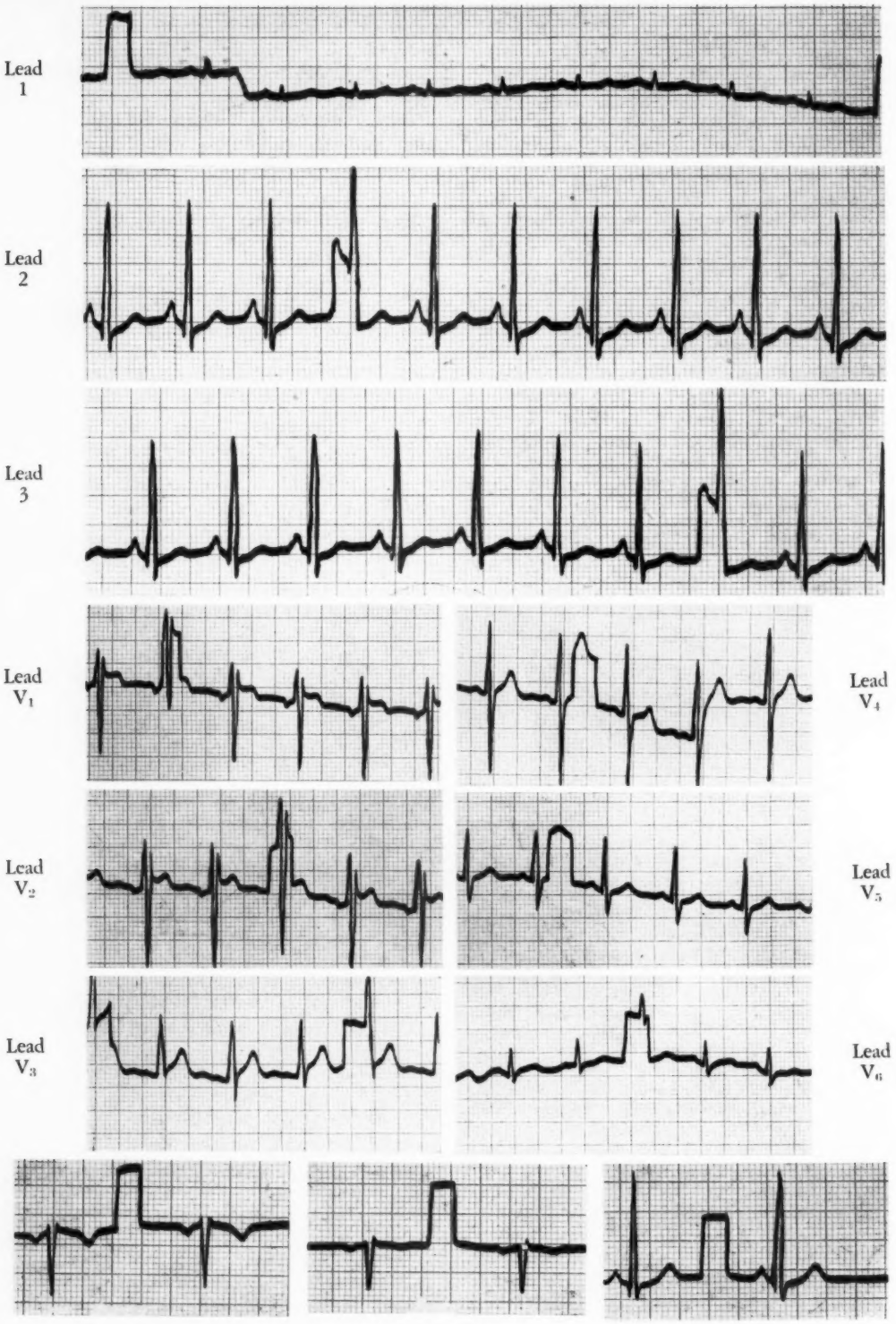
He was readmitted on June 6, 1944, because of a recurrence of his symptoms of fainting and weakness. These symptoms had developed several months following the first operation. On this admission his blood pressure was 118/80; respirations, temperature, and pulse were normal. Examination revealed that carotid sinus pressure on the right produced no changes. However, when digital pressure was applied over the left carotid sinus, the patient promptly collapsed.

Atropine 1/100 gr. was administered hypodermically and twenty minutes later the following tests and results were obtained:

PRESSURE TESTS	PULSE	RESPIRATION	BLOOD PRESSURE
Resting	80	24	118/80
Pressure over the right carotid sinus	80	24	118/80
Pressure over the left carotid sinus	40	28	70/?

On June 19, 1944, the left carotid sinus was stripped. This gave complete relief of syncopal attacks. There was no residual blood pressure or pulse abnormalities. This patient was again admitted to the Gallinger Hospital on May 21, 1945, for an unrelated condition. There had been no recurrence of symptoms, nor was there any evidence of hypersensitive sinuses. His blood pressure was 160/100, and there was no postural hypotension.

NORMAL PREOPERATIVE TRACING



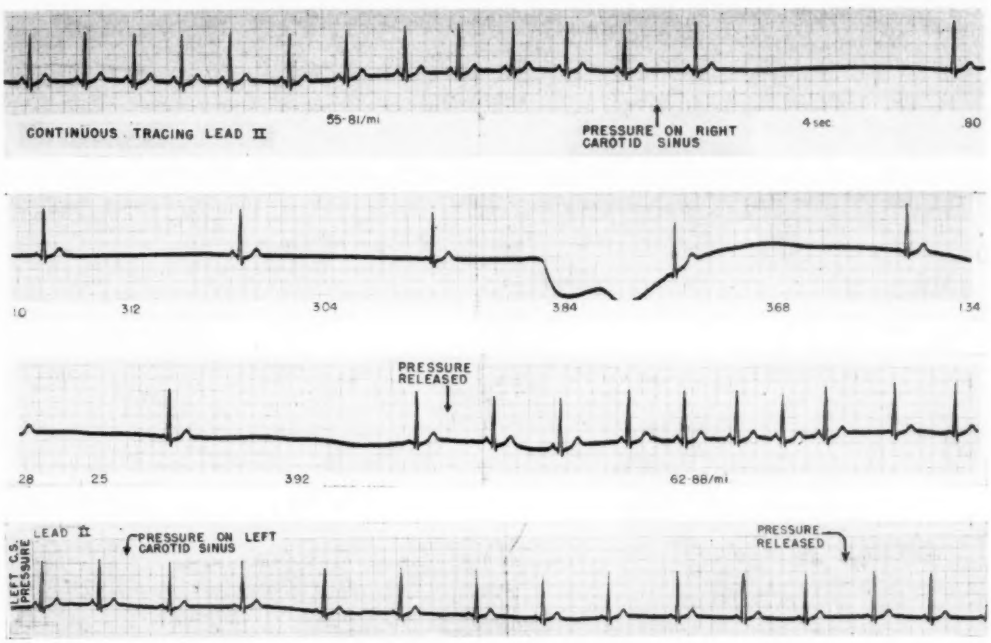


FIGURE 6. A continuous tracing (Lead II) showing the cardiac slowing produced by pressure over the right carotid sinus with the return to normal rate and rhythm when the pressure is released. Note the absence of any cardiac slowing when pressure is applied over the left carotid sinus. The small numerals under the tracing represent the duration of asystole.

THE above cases were of particular interest because each presented attacks of syncope and was examined in a hospital. However, in each instance the true nature of the condition was not determined on initial study. Undoubtedly the diagnosis was not made simply because the possibility of a hypersensitive carotid sinus reflex was not considered.

Case 2 should be particularly emphasized because repeated minor manifestations followed the first attack. It must be remembered that syncope is not the only effect of a hypersensitive carotid sinus reflex. Attacks of dizziness and weakness may be just as significant as the more formidable "blackouts."

Case 4 was unusual in that very shortly after the right carotid sinus had been denervated, the left became hypersensitive. Some authors have found that bilateral denervation caused postural hypotension. However, this did not occur in this instance.

The treatment of a hypersensitive carotid sinus reflex will depend on the frequency and severity of the reactions. All associated abnormalities should first be treated and if the patient is taking digitalis, this should be decreased if possible. Any localized glandular enlargement due to syphilis or tuberculosis should be treated with specific therapy. The patient should be instructed regarding fatigue, emotional upsets, tight collars, etc.

The vagal type is due principally to excessive vagal stimulation and may be controlled with large doses of atropine, or with ephedrine.[17,18] If these do not control the syncopal attacks, or if the patient cannot tolerate the drug, the carotid sinus should be denervated.

In the depressor type, which is due to a reflex vasodilatation through the aortic depressor nerves, atropine is useless. However, ephedrine or epinephrine may be effective.

In the cerebral type drug therapy has no ef-

FIGURE 5 *(opposite page)*. A normal tracing except for the triphasic QRS complexes in V_1 and V_2 which may indicate defective conduction in the right bundle of His.

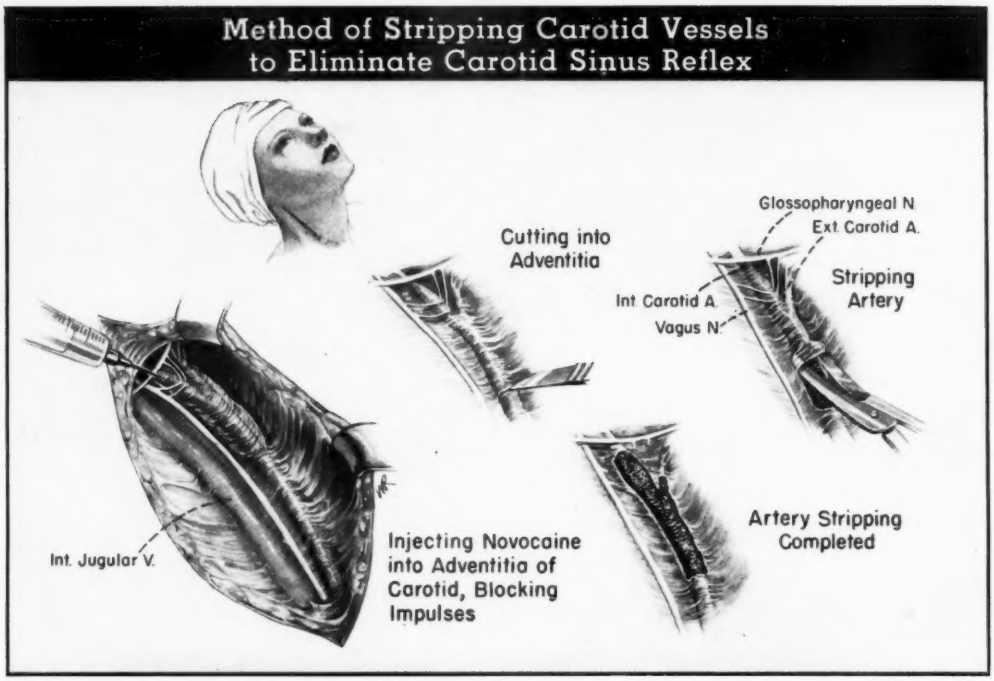


FIGURE 7. A diagram presenting the surgical technic of carotid sinus denervation.

fect. These cases should be treated by carotid sinus denervation.

There are many reports in the literature on the effects of carotid sinus denervation, and the results are invariably good.[3, 6, 7, 19, 20] We feel that unless drug therapy completely relieves the symptoms common to this condition denervation of the sinus is indicated. It is not enough to find that the attacks have diminished in severity and frequency through the use of drugs. We have shown that the minor manifestations of dizziness and weakness may be as serious as an actual syncopal episode. Denervation of the carotid sinus is a safe procedure when properly performed. The technic of the operation is as follows:

Denervation of the carotid sinus is usually performed under local anesthesia. The skin along the anterior border of the sternocleidomastoid muscle is infiltrated with novocain (1 per cent). An incision is then made, about 4 inches in length, through skin and platysma muscle. The sternomastoid muscle is retracted laterally and the carotid vessels exposed.

The internal jugular vein is retracted medially and the common carotid and vagus nerve identified. The common carotid is followed upward exposing the bifurcation and external and internal branches. The adventitia of these vessels is then infiltrated with novocain (1 per cent) to block the carotid nerve. This allows free manipulation without producing an attack of syncope. The adventitia of the upper portion of the common carotid, the lower segment of the external and internal carotid arteries is then completely removed. It is necessary to strip all of these segments and divide the sinus nerve in order to denervate the sinus completely.

Great care should be used in stripping the intercarotid tissue and the bulbous portion of the internal carotid. It is easy to tear the thin sinus area. In many of these cases the artery has already been damaged by arteriosclerosis and a repair may prove difficult. One must also be careful not to damage the vagus or glossopharyngeal nerves during the procedure.

When the intercarotid nerve is sectioned, a distinct increase in the blood pressure and heart

rate occurs, but these changes are usually only temporary.[6, 21-25] This effect is only temporary because the other cardiovascular regulatory mechanisms soon gain control. A postural hypotension may follow bilateral carotid sinus denervation.[25] Complete denervation will abolish all of the manifestations of the hypersensitive carotid sinus reflex. However, Weiss[7] has reported that the results in patients with severe neuroses and low metabolism may not be satisfactory, although the syncopal attacks are abolished. The symptoms incidental to the neurosis and low metabolism will persist.

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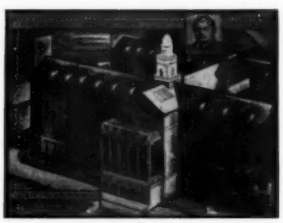
A HUNDRED YEARS OF EXPANSION



WHEN DR. NOBLE YOUNG and his colleagues, Drs. Charles H. Lieberman, Johnson Eliot and Flodoardo Howard, convened the first session of the Georgetown Department of Medicine (with Dr. Young as president) in October, 1850, two upper floors of a building at 12th and F streets in Washington accommodated the entire school. An old building on the grounds was converted into an infirmary with six beds.

As the Medical College continued to grow over the years, it was moved successively to 10th and E streets, 920 H street, and finally, in 1930, to its present splendid site high on a hill above Reservoir Road.

Near the colonial, red brick Medical-Dental Building, pictured in Edmund Kopietz' cover painting, stands the new Georgetown University Hospital, a direct descendant of the small infirmary at 12th and F streets. Dedicated to the service of humanity and the training of physicians who will further that ideal, the Medical Center of Georgetown University looks forward to continuing the work started a hundred years ago by Dr. Young and the other men who petitioned for the privilege of constituting the Medical Department of Georgetown College.

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Common Problems in Coronary Artery Disease

STEPHEN N. JONES[1] AND THOMAS F. KELIHER[2]

GEORGETOWN UNIVERSITY MEDICAL CENTER, WASHINGTON, D. C.

THE topic at hand is a complex one, one which has perforce elicited the interest of all physicians and most laymen and one, moreover, in which, despite recent advances in knowledge, controversy still unfortunately or perhaps fortunately rages.

Since it is manifestly impossible to cover the field adequately or bring forth new ideas, we shall attempt to limit ourselves to a discussion of common problems in coronary disease, and have attempted to call on literature and experience for practical points which may aid in their solution.

DIAGNOSIS IN CORONARY ARTERY DISEASE

Despite all technical advances the history is still the *sine qua non* in diagnosis. Pain is the cardinal symptom; it is ischemic in type and has the same characteristics as ischemic pain elsewhere. The most characteristic feature of this pain is its relation to stress, except when infarction has occurred, which in most instances occurs while at rest.[1]

The pain of ischemia is not usually related to motion as such or to respiration or posture. It is characteristically substernal with or without radiation to the shoulders, the ulnar nerve distribution in the arms, the back, the jaws, and the epigastrium. The left shoulder and arm are the commonest sites of radiation, while extension into the neck or jaw is considered practically pathognomonic. Cases without substernal element are rarely seen, although this factor may be ignored in the presence of significant pain at one of the sites of radiation. Occasionally the only manifestation is high left precordial or axillary pain, which is of definite significance in the absence of local tenderness and when the relation to stress is perceived. Localized periapical pain is extremely rare except in psychosomatic disorders or perhaps in pericarditis.

The character or quality of the pain is fairly constant though variously described as crushing, burning, tearing, etc.; the predominant element seems to be one of pressure, which might best be recalled by the picture of a man who was once seen by one of the authors immediately after a myocardial infarction. The patient was stretched over the back of the seat of the car and his hands still grasped the lapels of his coat and shirt and the loosened buttons gave mute testimony of his attempt to relieve the sense of pressure. The severity and duration of the pain roughly parallel the degree and duration of the ischemia and serve as an useful index of the changes resultant from ischemia.

Two useful but frequently overlooked points in the analysis of pain when infarction has occurred are (1) its wave-like qualities, and (2) the behavior response of the patient to his pain, so well delineated recently by McCleod.[2] We are all familiar with this restless attempt of the patient with infarction to "get away" from his pain.

[1]Chief Resident in Medicine, Georgetown University Hospital; Instructor in Clinical Medicine, Georgetown University Medical School, Washington, D. C.

[2]Associate Professor of Clinical Medicine, Georgetown University School of Medicine; Associate Visiting Physician, Georgetown University Hospital, Gallinger Municipal Hospital, and Providence Hospital; Consultant, U. S. Air Forces, Bolling Field, Washington, D. C.

A significant exception to the above rule should be noted, one largely ignored in the past, i.e. coronary artery disease in the Negro. It has been repeatedly stated that angina does not occur in the Negro, and statistically it is rare. This has been explained as an inability to feel or to express pain on the part of the Negro, but there is little evidence to support this contention.

On the other hand, Hunter[3] has theorized that the lack of pain is due to the earlier onset and greater severity of hypertension in the Negro race with its concomitant dilatation of the coronary collaterals. In the same paper Hunter has shown that the Negro most frequently manifests his myocardial infarction by the sudden onset of dyspnea or the sudden increase in an already existing dyspnea, and this has been confirmed by Libman[4] who describes such symptoms under the title of "substitution symptoms." Under this title he has also placed such symptoms as dizziness, fatigue, vertigo, nausea, vomiting, palpitation, syncope, etc., and he explains such manifestations on the basis of an increased threshold to pain. Carefully observing these symptoms, Kugel[5] noted that up to 97 per cent of all patients with myocardial infarction manifested pain or one of its substitutes.

Having once determined, largely by history, the presence of myocardial ischemia, the evaluation of its consequences proceeds by physical examination, the electrocardiogram, the usual laboratory procedures, ballistocardiogram, and possibly by roentgenkymography. In regard to physical examination it is to be noted that despite the "radical drop" in blood pressure of the texts, the man on the spot seldom sees this early, but rather a normal or elevated blood pressure which, however, is extremely labile on frequent determinations. A significant drop may not occur for 24 hours or more.

Despite the controversy over its terminology, Master's concept of the types of ischemia has been an extremely useful guide in evaluating the effects of ischemia and in reminding us that many cases with typical long-continued coronary type pain may have little or no element of coronary narrowing and can be treated simply by correction of other underlying physiologic disturbances. He has also led us to a more intelligent use of the nitrates.[6]

STEPHEN N. JONES THOMAS F. KELIHER

TREATMENT

As to the treatment of angina there seems to be little controversy and we are given time to work the problem out step by step; the same applies to a lesser extent to so-called coronary failure[7] or insufficiency and we are here sternly reminded by Master[6] that this is an entity which *can* be treated. However, in the treatment of myocardial infarction, as is to be expected in a disease which has so many elements beyond our influence, we are beset by numerous knotty problems and the distractions of controversy.

Treatment of pain is a primary consideration. Morphine in physiologic doses and demerol are standard drugs. Gold stresses the fact that the dose of morphine is 1/6 gr. If pain is extreme and appears to be leading to shock, there seems to be no valid objection to careful intravenous administration of morphine. However, in the presence of cor pulmonale, marked pulmonary emphysema, asthma, or a kyphoscoliotic chest, morphine must be avoided and demerol should be substituted. Oxygen, if available, is an extremely valuable adjunct as is reassurance, if possible.

The intravenous use of papaverine has its advocates, but its physiologic action is evanescent and reactions are not rare. Atropine and large doses of xanthines, though useful in the tremendous doses used in animal experimentation,[8] seem to have no effects in the small doses tolerable by man. In the initial phases opiates for pain and sedatives for restlessness and apprehension are safe standards. Xanthines by mouth have no proved effect and cause nausea even in well persons.

In the rare case complicated by acute left ventricular failure, rapid digitalization and use of

mercurials is indicated; in the usual case with auscultatory findings indicating basal pulmonary edema and mild respiratory difficulty, the mercurials alone are usually effective and perhaps safer. Routine use of quinidine for prevention of arrhythmias appears to have no disadvantages and is indicated where there is evidence of ventricular irritability.

The brilliant work of Prinzmetal,[9] which has shown that if pressure is maintained in the sinuses of Valsalva, almost any degree of arterial occlusion can be survived, appears to offer new hope in those highly fatal cases in which shock ensues. Thus far, attempts to maintain this pressure by intravenous fluids and transfusions have been of little avail;[10] perhaps intra-arterial transfusions and pressure suits will be the answer.

Bed rest, how much and how long, is still a moot question and the last analysis depends on our estimate of the size of the infarction, as aided by clinical, laboratory, and electrocardiographic methods, and the presence or absence of collateral circulation as judged largely by age and history. In the relatively young patient with a large initial infarction maximal bed rest for 6 weeks or more is indicated; in old patients or those having repeated infarctions, the areas are usually smaller in those who survive and collateral circulation seems better; thus 2 or 3 weeks are often adequate.

Except for patients in shock, there seems to be no valid objection to being helped to a bedside commode. Most patients can turn themselves and feed themselves after the first few days, if properly instructed. All should be trained in foot and diaphragm exercises. Safe criteria for mobilization appear to be absence of congestive heart failure, return of the S-T segments to the baseline, and normal sedimentation rate. The latter, however, can very seldom be obtained in the old, and in younger patients appears to be frequently due to a mural thrombus and probably is not a valid reason for excessive protraction of bed rest.

One of the most common complications of myocardial infarction is cardiac neurosis, and it is obvious that the longer and more rigid the bed rest, the more likely the development of a cardiac neurosis. Would it not also seem that metabolism might be at a higher ebb during unhappy recumbency than at satisfied sitting in a comfortable chair? Thus we are reminded by Harrison, et al.[11] that prolonged bed rest following myocardial infarction has more serious psychic disadvantages than physical advantages.

ANTICOAGULANTS

The apparently impressive reduction in mortality (13 per cent) revealed in Wright's monumental survey of the effects of anticoagulants, although factual, demands critical individual evaluation.[12] The pressure of poorly informed public opinion should not lead us to its use in any case in which we are uncertain as to its safety by reason of inadequate laboratory control, history of bleeding, suspicion of or proof of hepatic insufficiency, or potential sources of bleeding, e.g. peptic ulcer. There appears to be absolutely no justification for the emergency use of dicumarol, even though some believe its efficacy lies in its spasmolytic action upon the coronaries.[13] One is always justified in obtaining baseline prothrombin levels and in delay for clinical appraisal. The interval use of heparin is in most cases optional.

In the present state of our knowledge it appears probable that dicumarol has its maximal efficacy in those cases in which there is an element of congestive heart failure, with attendant slowing of circulation time, venous stasis, and chronic hypoxia, i.e. the more severe cases.[14] In those cases in which its use is not feasible, or in those in which its use is decided against for other valid reasons, there seems at present to be no reason why comparable results cannot be obtained by measures directed against thromboembolic phenomena by other means. The use of anticoagulants is therefore most strongly indicated in those cases in which there is an element of congestive heart failure and in which, by reason of continued, otherwise unexplained fever, suspicion of a large mural thrombus arises. Anticoagulants should be continued for a period of 4 to 6 weeks according to the indications for their use.

AFTER CARE

Here again a knotty problem is aggravated by being conducted under the eye of an opinionated public and our fear of the intangible elements inherent in the disease.[15] Our only real criteria for rehabilitation are our estimate by clinical and electrocardiographic means of adequacy of initial healing, our estimate of cardiac reserve by performance, and the confidence of the pa-

tient. In spite of the fact that return of electrocardiographic changes towards normal continue at times for a year or more, one must bear in mind that for the average patient anxiety over the future and his financial security or lack of it may impose a far greater strain upon the circulation than the quiet performance of remunerative but not strenuous work. We should have no guide but an honest and well-considered opinion as to what seems best for the individual and his family. By this time we should know the patient well enough to be able to determine whether or not he is one of that large group of individuals with organic heart disease whose personality pattern is such that anxiety is met with increased cardiac output, and to determine in which direction the sources of that anxiety lie.

INDUSTRIAL AND INSURANCE COMPENSATION IN MYOCARDIAL INFARCTION

Probably the most controversial issue in medical practice is that of the financial compensability of persons with myocardial infarction. No problem is raised by the white-collar worker who develops his infarction while on a vacation or after a social whirl, but the laborer who, while actually doing manual labor, develops chest pain and the signs of myocardial injury is often considered eligible for compensation. It is of course well known that most coronary thromboses occur at rest.[16] However, precipitation of myocardial injury in the absence of actual coronary thrombosis, especially under circumstances of unusual strain, could well be considered from the medical standpoint worthy of consideration for compensation, especially if anatomic proof is available.

In 1939 Boas[17] carefully reviewed 14 cases of myocardial infarction due to effort or trauma to the chest wall. In commenting on these cases, 5 of which were considered compensable, the author states that a man who is previously free of symptoms or who has well compensated angina, is compensable provided his symptoms began immediately after the exertion or trauma, or, if delayed for several weeks, there is a continuity of symptoms dating from the event to the time of the complete disability. A review of the supposed pathology in such cases was given, i. e. that effort or trauma causes intimal hemorrhage and subsequent thrombus formation.

In contrast to these studies and views, Master, et al.[16] state that coronary occlusion is the end result of arteriosclerosis and no effort or trauma or emotion will produce it. Further he has shown that intimal hemorrhage occurs as frequently in the nonactive as in the active, and in a careful review of 1,700 cases of coronary occlusion and infarction he has found it to be as frequent in the sedentary as in the physically active. On the other hand he does not deny that direct trauma to the chest wall may precipitate myocardial injury.

Thus in all fairness to the individual concerned and in consideration of the potential hazard of a large group of our older population being eliminated from gainful employment by rigid insurance requirements, there is a need for an authoritative clarification of present terminology and definition and delineation of standards under which cases might be considered eligible for financial compensation.

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Carcinoma of the Upper Rectum and Rectosigmoid

CLINICAL REPORT ON HIGH INFERIOR MESENTERIC LIGATION

GARNET W. AULT,[1] A. F. CASTRO,[2] AND ROBERT S. SMITH

GEORGETOWN UNIVERSITY SCHOOL OF MEDICINE, WASHINGTON, D. C.

We wish to discuss three subjects related to the surgical treatment of carcinoma of the rectum and rectosigmoid. During the present "controversy" regarding sphincter-saving operations versus the conventional Miles abdominoperineal resection, we have been impressed by the lack of clarity and the fundamental understanding of these subjects.

Therefore, we would like to present a re-evaluation of the surgical anatomy of the inferior mesenteric vessels and their collaterals; we wish to re-emphasize some of the concepts of lymphatic spread; we also would like to present some clinical material and make recommendations regarding high ligation of the inferior mesenteric vessels and methods of diagraming resected specimens. This clinical material has been obtained during a review of 235 cases of carcinoma of the rectum and the rectosigmoid that have come under our observation and care.

SURGICAL ANATOMY

The report of Sudek[6] in 1907, in which he defined the "critical point" of ligation of the superior hemorrhoidal artery, has influenced surgical anatomic technic to this day. However, many surgeons have failed to realize that Sudek was discussing this problem in its relationship to *perineal resection of the rectum*. Miles' work was not published until 1908.[7] Sudek made his report after experiencing the development of gangrene of the upper rectum in 2 patients whose superior hemorrhoidal arteries had been ligated during perineal resection just distal to the last sigmoid branch of the inferior mesenteric artery (S_3, Figure 1).

In Sudek's subsequent cadaver studies he ligated the superior hemorrhoidal artery just proximal to the last sigmoid branch (S_3) and injected material into the inferior mesenteric artery near its origin. This material passed through the sigmoid arcades and marginal artery and appeared in the distal rectal branches of the superior hemorrhoidal artery. When he ligated the superior hemorrhoidal artery *distal* to the last sigmoid branch (S_3), the material did not appear in the distal rectal branches of the superior hemorrhoidal artery. As a result of these studies, he recommended laparotomy and ligation of the superior hemorrhoidal artery *proximal* to (S_3). He advised this so that greater mobilization of the rectum could be obtained and a more accurate high ligation could be achieved. These specific recommendations were presented in reference to perineal resection of the rectum, or some modification thereof, in which the proximal bowel was brought down as a perineal anus. It should be emphasized that this "critical point" was not intended to have any relationship to the Miles abdominoperineal resection or to anterior resection.

Hartmann[10] in 1909, referring to perineal resection of the rectum, verified Sudek's work but placed the point of ligation just below the promontory of the sacrum. The subsequent fine anatomic and surgical studies of Archibald,[8] Rubesch,[11] Drummond,[12, 13] Pope and Judd,[17] Steward and Rankin,[20] Sunderland,[27] Bacon and Smith,[31] and Muir[34] have been reviewed. This was done for there is a great need for clarification of certain points. Furthermore, there is need for more specific and exact information on the functional capabilities of the rectal and colonic blood supply in the living.

From the Department of Proctology, Georgetown University School of Medicine.

[1]Professor of Proctology, Georgetown University School of Medicine, Washington, D. C.

[2]Assistant Professor of Proctology, Georgetown University School of Medicine, Washington, D. C.

GARNET W. AULT

A. F. CASTRO

ROBERT S. SMITH

The investigators mentioned above have clearly demonstrated that the marginal artery is uninterrupted in its functional continuity from the cecum to the lower sigmoid. There is evidence that the marginal artery can be filled in its entirety by material injected through the superior mesenteric artery following ligation of the inferior mesenteric artery (Sudek,[6] Rubesch[11]). It also may be filled with material injected through the inferior mesenteric artery following ligation of the superior mesenteric artery (Drummond[12,13]). If this evidence is correct, and we feel that it is, the marginal artery is capable of supplying the distal colon including the upper sigmoid, when the inferior mesenteric artery is ligated at its origin. This point of ligation is proximal to its first branch, namely the left colic (L.C.) or conjointly the left colic (L.C.) and first sigmoid (S_1) (Figure 1). Lest there be any misinterpretation of this statement, we wish to point out clearly that it is made in reference to the surgical removal of carcinoma of the rectum and/or rectosigmoid utilizing the Miles abdominoperineal resection, anterior resection, or the Babcock-Bacon method of resection.

The blood supply of the rectum is derived from the superior hemorrhoidal artery, the middle hemorrhoidal arteries from the internal iliac arteries, and the inferior hemorrhoidal arteries from the internal pudics. Because of the free anastomosis between all of these vessels, it has been difficult to investigate the blood supply of the rectum below the peritoneal reflection. However, all experienced rectal surgeons are aware of the variable size and functional capabilities of the middle hemorrhoidal vessels. During rectal resections, when the rectal stalks are cut, these middle hemorrhoidal vessels are clamped and ligated if they are large; they are frequently ignored if they are small and the bleeding ceases rather promptly. On the other hand, one invariably has to ligate the inferior hemorrhoidal vessels. This indicates that the collateral blood supply of at least the lower 4 inches of the rectum is greater than we surgeons sometimes appreciate or will acknowledge.

The most recent satisfactory surgical anatomic study supporting, in part, the aforementioned evidence has been made by Goligher.[36] In contrast to Sudek's studies which were applicable to perineal resections, Goligher's investigations are applicable to the classical Miles[7,16,25] abdominoperineal resection and to anterior resection. We feel that they are also applicable to the Babcock-Bacon proctosigmoidectomy[29] and to other methods[28] of rectal resection. Goligher's studies of the inferior mesenteric artery were carried out during Miles and anterior resections in 36 patients. He also studied the inferior mesenteric vessels in 75 cadavers.

Figure 1, redrawn from Goligher, illustrates the most common arrangement of the inferior mesenteric artery. This diagram and these average measurements are of the utmost importance. In 40 cadavers the left colic (L.C.) and first sigmoid (S_1) arose conjointly 1½ inches from the aortic origin of the inferior mesenteric artery. This point of conjoint origin was at the lower edge of the aortic bifurcation and 2½ inches proximal to the sacral promontory. In 30 specimens the first sigmoid (S_1) arose separately ½ to ¾ inch distal to the left colic (L.C.), and this point of origin would therefore be from 2 to 1¾ inches proximal to the sacral promontory.

These average measurements are important for the acceptable point of ligation of the inferior mesenteric artery in this country has, with rare

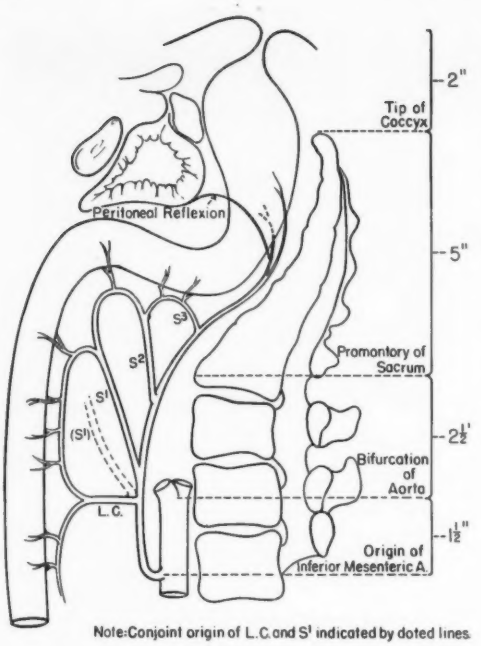

FIGURE 1. Diagram illustrating the most common levels at which the various branches of the inferior mesenteric artery arise. Measurements are related to the origin of the inferior mesenteric artery, the caudal edge of the aortic bifurcation, and the promontory of the sacrum.

exceptions, been placed just at or above the point where it crosses the left common iliac artery. This point is almost invariably just proximal to (S_2) despite the fact that Miles[7] stated, "The inferior mesenteric artery is then ligatured below the point where it gives off its uppermost branch to the pelvic colon." Unless we are in error regarding our observations during clinical tours and our interpretation of the level of ligation indicated by some of the writers on the subject, we have been impressed by the low level of ligation of the inferior mesenteric artery or ligation of the superior hemorrhoidal artery. As a result we have come to the conclusion that 2 inches and sometimes 3 inches of these vessels and glands have been left on the patient instead of being removed with the specimen. This compromising ligation is and has been done despite Miles' recommendations. In the past years it is evident that surgeons have paid too much attention to Sudek's point and too little attention to Miles' advice.

LYMPHATIC SPREAD

It is entirely probable that the clinical observations and studies of Miles have had as much influence on surgical effort in the field of lymphatic spread as the work of Sudek has had regarding the superior hemorrhoidal vessels. However, if one reads Miles' original article,[7] it is to be noted that "until the close of the year 1906 I had relied solely upon the perineal method of excision of the rectum."

On December 19, 1908, he published "A Method of Performing Abdominoperineal Excision for Carcinoma of the Rectum and of the Terminal Portion of the Pelvic Colon."

Miles was not satisfied with the methods of resection practiced in his day, and he wished to "bring the operation of excision of the rectum into line with those methods of performing abdominal hysterectomy known as the Wertheim and the Krönig-Wertheim." His greatest concern was the zone of upward spread. To this end we quote, "So far as I have been able to gather from the literature on the subject, however, the technic of these operators seems to have failed in one respect—namely, the complete eradication of the zone of upward spread of cancer of the rectum, whereby the chance of recurrence of the disease, above the field of operation, can be diminished if not entirely obviated." Because Miles was concerned about the upward zone of spread, he advised, "The inferior mesenteric artery is then ligatured below the point where it gives off its uppermost branch to the pelvic colon." Judging from the diversified descriptions of operative procedures in the current literature, the level of ligation recommended by Miles and the erroneous conception of Sudek's point have been compromised by ligating these vessels "on," "near," or "just above" the promontory of the sacrum. Miles was probably aware of the lymphatic studies of Quénu,[1,3] Gerota,[2] Delamere, Poirier, and Cuneo,[4] and Jamieson and Dobson.[5,9]

The numerous investigations on lymphatic drainage published subsequent to Miles' original article have modified our concept of lymphatic metastasis. It is necessary to omit a review of the following reports: McVay,[14] Villemin, et al.,[15] Dukes,[18] Wood and Wilkie,[19] Westhues,[21] Gabriel, Dukes, and Bussey,[22] Gilchrist and David,[23] Grinnell,[24] Coller, Kay, and MacIntyre,[26] Glover and Waugh,[30] Gilchrist and David,[33,35] and Bacon and Rowe;[32] but we wish to make note that Westhues,[21] in 1934, was the first to indicate that the retrograde lymphatic spread of metastasis from rectal carcinoma was the exception rather than the rule. As a result of Westhues' report, the entire subject has been actively investigated.

The reports of Gilchrist and David,[23,33] Coller, Kay and MacIntyre,[26] and Glover and Waugh[30] are of particular interest for they indicate that retrograde lymphatic metastasis occurs, with rare exception, only when the proximal nodes along the superior hemorrhoidal and the inferior mesenteric

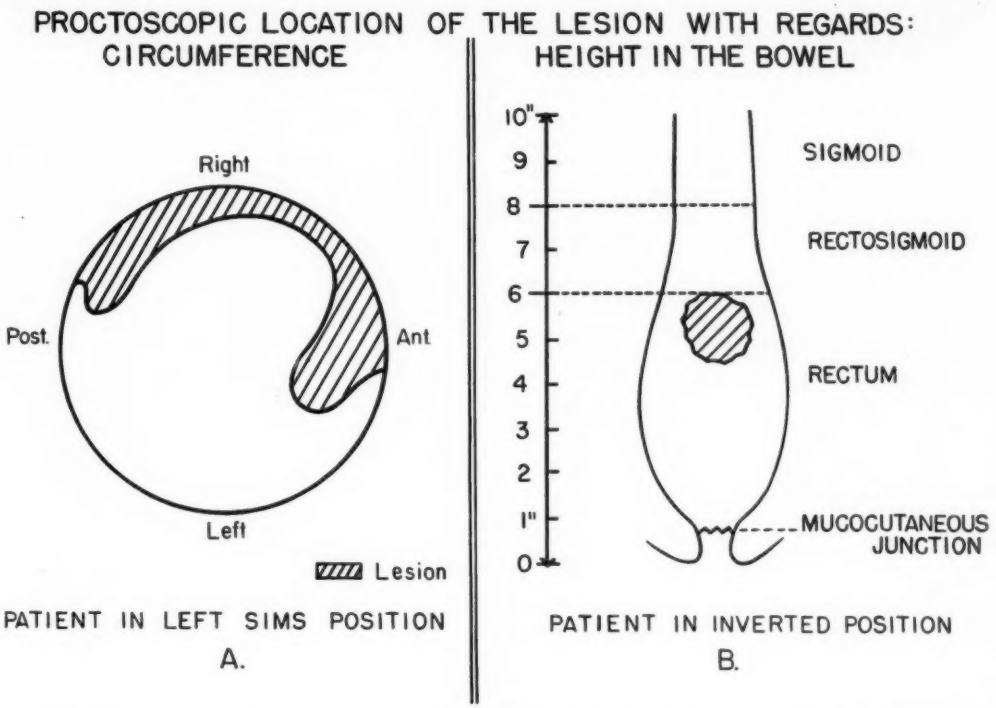

FIGURE 2. Diagram illustrating (A) the location of the lesion and its degree of infringement on the diameter and circumference of the bowel lumen; (B) the level of the malignancy as measured from the mucocutaneous junction to the caudal edge of the lesion.

vessels are choked with metastasis. In this event retrograde and lateral spread along the middle hemorrhoidal vessels may occur when the lesion is located in the upper rectum (intraperitoneal carcinoma of the rectum—Gilchrist[33,35]).

It is not our purpose to enter into the controversy regarding downward, lateral, or retrograde spread. Attention has been called to the work that has been done in this field. However, it is our feeling that the zone of upward lymphatic spread has been lost sight of during the controversy regarding the radicability of the Miles versus the sphincter-saving operations. Therefore we wish to present this clinical report on high inferior mesenteric ligation.

MEASUREMENTS

THERE is need for an acceptable method of accurate anatomic measurements and drawings indicating the exact location of the malignancy of the rectum. This is especially true of the upper rectum and rectosigmoid due to the mobility of lesions at this level. Three sets of measurements are used by us: (1) before operation, (2) during operation (a) the peritoneal level, (b) the distance between the aortic origin of the inferior mesenteric artery and the site of ligation is recorded, (3) after operation—the resected specimen.

Before operation a digital measurement is made with the patient in the lateral Sims position. The degree of downward intussusception and fixation of the lesion is digitally estimated before inverting the patient. The distance from the mucocutaneous junction to the lower edge of the malignancy is recorded (Figure 2b). During proctoscopy most measurements are made in the inverted Hanes position and not in the knee chest position. A few patients are measured in the elevated lateral Sims position. This proctoscopic distance is correlated with the digital distance. Surgeons should be interested in the length of available rectum distal to the lower edge of the lesion. Carcinoma of the rec-

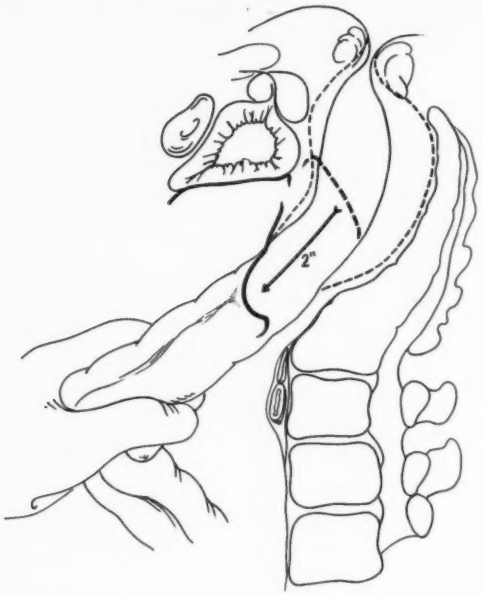

FIGURE 3. Diagram illustrating how the peritoneal reflection is elevated following dissection of the rectum from the hollow of the sacrum. The rectal stalks have been cut and the rectum has been dissected anteriorly. The rectum can then be pulled upwards (cephalad) and forward in almost a straight line from the levator.

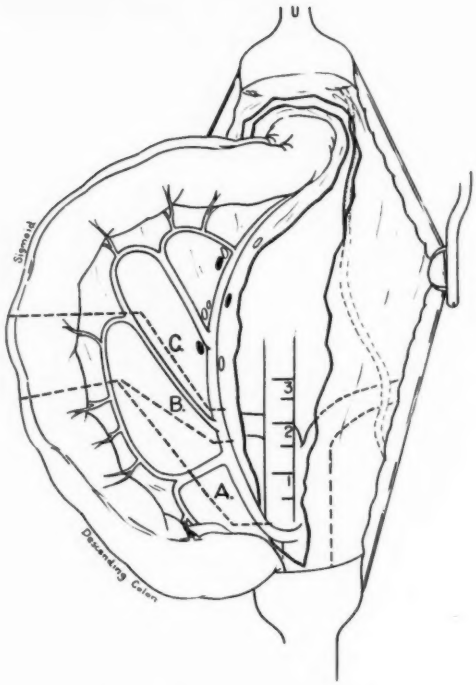

FIGURE 4. Diagram illustrating exposure of the aortic origin of the inferior mesenteric artery. The ruler is inserted to measure the distance from the origin of the inferior mesenteric artery to the point of ligation. The ligation and dissection of the mesentery may extend along zone A, B, or C depending upon the various factors mentioned in the article.

tum is defined as those lesions arising in the zone between the mucocutaneous junction and a point 6 inches proximal to it. Carcinoma of the rectosigmoid is defined as those lesions arising in the zone 6 to 8 inches above the mucocutaneous junction. Figure 2a indicates whether the lesion is located on the anterior, posterior, or lateral edge of the bowel. The degree of obstruction is noted. The size of the lesion is estimated, and other descriptive information is recorded. From this initial information we indicate whenever possible what type of resection we expect to perform.

During operation (a) we believe that the variable level of the anterior peritoneal reflection in both sexes is of limited value in determining the location of the rectosigmoid. The rectosigmoid means a different section of the bowel to different surgeons. The upper rectum and rectosigmoid are mobile structures, and their relationship to the sacral vertebra is variable in the presence of malignancy. We have, therefore, adopted the suggestion of Gilchrist that we "feel" that a lesion is a carcinoma of the intraperitoneal rectum or a carcinoma of the rectosigmoid. The peritoneal level is conceded to be of value in relationship to lymphatic spread and local invasion (Coller,[26] Gilchrist[23, 33, 35]). However, the peritoneal level, following elevation of the rectum from the hollow of the sacrum, may be brought 2 or even 3 inches cephalad to its original location (Figure 3). As a result, the surgeon is most interested in the length of the rectum distal to the lower edge of the lesion if anterior resection is contemplated. The relation of the lesion to the peritoneal level is recorded.

(b) Measurements of the inferior mesenteric artery are made during the operative procedure. An orderly pattern of examination is carried out. Palpation and/or visualization of all abdominal viscera precedes the examination of the lesion itself. The accessible lesion is palpated to

determine local resectability. The origin of the inferior mesenteric artery is next examined through the right leaf of the mesentery without opening the peritoneum. The peritoneum is then opened on both sides of the mesentery by an incision that is carried cephalad to expose the aortic origin of the inferior mesenteric artery. This can be satisfactorily accomplished in over 80 per cent of cases where it is attempted. The greatest handicaps to this maneuver have been inadequate exposure with anesthetic problem cases, a fat mesentery, a shortened mesentery "choked" and involved with diffuse metastasis or in a poor risk patient in whom the operative time is a factor.

In the majority of cases, the vessels were exposed, and the adventitia and glands were stripped off in a downward distal fashion for a distance of 1 to 2 inches. This zone of exposure extends from the aortic origin of the inferior mesenteric artery distal to the origin of the left colic (L.C.) and first sigmoid (S_1). This zone of exposure extends for 1½ to 2 inches above or cephalad to the lower edge of the bifurcation of the aorta. The inferior mesenteric vessels are thus individually identified. The vein is usually found within ½ inch to the left and dorsal to the artery. In most cases the left colic (L.C.) and first sigmoid (S_1) come off conjointly, or (S_1) arises within ¼ to ½ inch distal to the origin of (L.C.) (Figure 4).

During this dissection the dense areolar tissue and intermesenteric nerve fibers in the lower obtuse angle between the aorta and inferior mesenteric artery are carefully dissected so that a stainless steel rule may be inserted. A point of ligation is selected and the distance from the aorta is measured (Figure 4). The vessels are clamped, cut, and tied. The abdominal phase of a typical Miles type of dissection is done. In over 90 per cent of the cases herein reported the middle hemorrhoidal vessels were sacrificed in order to obtain exposure and elevation of the lower rectum.

After operation, the freshly resected specimen is opened and it is allowed to assume a relatively normal contour. In most instances the flat mucosal pattern of the rectum is evident, and the corrugated mucosal pattern of the sigmoid is readily seen. We are then able to localize visually the exact site of origin of the lesion, and this is correlated with the proctoscopic and estimated site determined by palpation before resection. Measurements are then taken (Figure 5), and the final location of the malignancy is recorded. The specimen is not fixed in any way until all these measurements have been made and correlated.

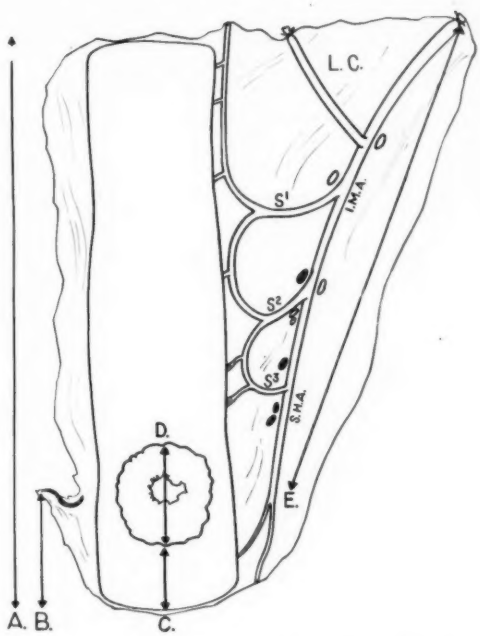

FIGURE 5. Diagram illustrating the freshly resected specimen. A. The total length of the specimen. B. The distance from the peritoneal reflection to the lower edge of the specimen. C. The distance from the lower edge of the lesion to the lower edge of the specimen. D. The diameter of the malignancy (to include the amount of free bowel on either side and the gross degree of penetration into or through the bowel wall). E. The distance from the site of ligation of the inferior mesenteric artery to the center of the lesion (to include the location of glands cleared for microscopy).

REPORT OF CASES

DURING a study of 235 cases of carcinoma of the rectum and rectosigmoid that is now in preparation, we found that we did *measured inferior mesenteric ligations* in 48 cases. We felt that 16 of these cases had not been ligated any higher than usual (2½ to 3 inch zone) so they have been rejected. However, 32 cases have been ligated in the zone measuring 2¼ inches or less distal to the aortic origin of the inferior mesenteric artery. All of these patients had a Miles type of abdominal dissection. At the conclusion

TABLE 1

CASE	LOCATION*	I.M.A. LIGATED AT	BRANCHES LEFT ON PATIENT	TYPE OF RESECTION
1	R.	Aorta	0	Miles
2	R.S.	Aorta	0	Ant. Resection—closed
3	R.S.	½ inch	0	Ant. Resection—open
4	R.	1 inch	0	Ant. Resection—open
5	R.	1 inch	L. C.—S_1	Ant. Resection—open
6	R.	1 inch	L. C.—S_1	Ant. Resection—open
7	R.	1 inch	0	Miles
8	R.	1½ inches	L. C.—S_1	Ant. Resection—open
9	R.	1½ inches	L. C.—S_1	Ant. Resection—open
10	R.	1½ inches	L. C.	Miles
11	R.	1½ inches	L. C.—S_1	Ant. Resection—open
12	R.	1½ inches	L. C.	Miles
13	R.S.	1½ inches	L. C.	Ant. Resection—open
14	R.	1¾ inches	L. C.—S_1	Miles
15	R.	1¾ inches	L. C.	Miles
16	R.S.	2 inches	L. C.—S_1	Ant. Resection—open
17	R.	2 inches	L. C.—S_1	Ant. Resection—closed
18	R.	2 inches	L. C.—S_1	Babcock-Bacon
19	R.	2 inches	L. C.—S_1	Miles
20	R.	2 inches	L. C.—S_1	Miles
21	R.	2 inches	L. C.—S_1	Ant. Resection—open
22	R.	2 inches	L. C.—S_1	Miles
23	R.	2 inches	L. C.—S_1	Sacral Anastomosis
24	R.S.	2 inches	L. C.—S_1	Ant. Resection—open
25	R.	2 inches	L. C.—S_1	Babcock-Bacon
26	R.	2 inches	L. C.—S_1	Ant. Resection—open
27	R.	2 inches	L. C.—S_1	Ant. Resection—open
28	R.	2 inches	L. C.—S_1	Ant. Resection—closed
29	R.	2¼ inches	L. C.—S_1	Babcock-Bacon
30	R.	2¼ inches	L. C.—S_1	Ant. Resection—open
31	R.	2¼ inches	L. C.—S_1	Miles
32	R.S.	2¼ inches	L. C.—S_1	Ant. Resection—open

*R.—Rectal carcinoma.
R.S.—Rectosigmoid carcinoma.

of this it was determined that the operation could be consummated as a Miles abdominoperineal resection in 12 (37.5 per cent) cases. A resection of the distal half of the sigmoid, the rectosigmoid and the upper rectum—an anterior resection—was done in 17 (53 per cent) cases. A Babcock-Bacon proctosigmoidectomy was done in 3 (9.3 per cent) cases, and in one case a low anastomosis was done through a posterior anococcygeal incision.

In all instances viable proximal bowel was obtained without difficulty for a colostomy, for an anastomosis, or for a pull-through procedure. In all instances of anterior resection the rectal stump remained viable, despite the fact that the middle hemorrhoidal vessels had been sacrificed in over 90 per cent of cases. Most of these anterior resections were done by an open method, without clamps, and frank bleeding from the cut edge of the rectum was a problem during the operation. No necrosis of the rectal stump developed, nor was it anticipated (Table 1).

In discussing Table 1 it will be seen that ligation of the inferior mesenteric artery (I.M.A.) *proximal* to the left colic (L.C.) and first sigmoid (S_1) was performed in 5 cases. Cases 1 and 2 were ligated on the aorta. Viable sigmoid, supplied by only the marginal artery, was obtained in all 5 cases. Two cases (1, 7) terminated as Miles resections, and 3 cases (2, 3, 4) terminated as anterior resections. Primary union ensued in all 3 cases.

Ligation of the (I.M.A.) distal to the origin of (L.C.) and proximal to the origin of (S_1) was done in cases 10, 12, 13, and 15. Cases 10, 12, and 15 terminated as Miles resections, and case 13 terminated as an anterior resection.

Ligation of the (I.M.A.) distal to the conjoint origin of (L.C.) and (S_1) or distal to the origin of (S_1) (which arose ½ to ¾ inch distal to the origin of L.C.) was done in all other cases. The table indicates how the operation terminated.

SPACE will not permit a detailed analysis of this table. However, it should be clear that there is some variation in the level at which the left colic and first sigmoid vessels come off the

(I.M.A.). It should also be evident that these ***measured high ligations*** permit one to remove an additional 1½ to 2 inch zone, or more, cephalad to the site of ligation recommended by Miles. This should result in an increase in the cure rate of malignancy in this location. We hope to report on this later with a control series. However, for obvious reasons, we do not recommend that the casual operator perform high (I.M.A.) ligation. We suggest that it undergo further trial.

SUMMARY AND RECOMMENDATIONS

1. We wish to recommend that the relationship of Sudek's "critical" point to current methods of rectal resections be minimized or even ignored.

2. By reference to the literature, the continuity of the marginal artery from the cecum to the upper sigmoid is pointed out. The clinical experience of Goligher[30] indicates its functional capabilities following ligation of the (I.M.A.) distal to (L.C.) and (S_1). Our clinical experience has demonstrated its functional capabilities follow ligation of the (I.M.A.) *both distal* and *proximal* to (L.C.) and (S_1). The visibility of the upper sigmoid, as maintained by only the marginal artery, is more constant than is generally appreciated. We recommend further clinical studies be made.

3. The bogey—necrosis of the rectum—perpetuated by some authors influenced by Sudek's work, should be buried. It should be understood that this applies to anterior resection for we have never experienced necrosis of the rectal stump complicating this procedure; neither have we heard it nor seen it authoritatively in print. We feel, with ample clinical experience and bibliographical evidence in the literature, that the inferior hemorrhoidal arteries and their collaterals are responsible for the viability of the rectum to a greater degree than has been heretofore stated. We wish to imply that this is true regardless of the status of the middle hemorrhoidal vessels. Therefore we would recommend that further clinical studies be reported on anterior resections in which high ligation of the inferior mesenteric vessels be combined with ligation of the middle hemorrhoidal vessels.

4. The work done by Goligher[30] merits further study, application, and adaptation to the current trends in rectal resection. As a result of Goligher's work and this clinical report, we recommend that the point of ligation of the inferior mesenteric artery be recorded by measuring the distance between the point of its aortic origin and the site of ligation. This recommendation is made for we feel that ligation "so many inches" proximal to the sacral promontory, ligation where the artery crosses the left common iliac, and ligation distal to the first sigmoid artery are vague, inaccurate terms.

5. It has been pointed out that the zone of upward spread appears to have been lost sight of during the current controversy regarding sphincter saving operations. The zone of retrograde downward and lateral spread will undoubtedly receive further investigative attention. For the present we feel satisfied that it occurs in upper rectal and rectosigmoid lesions only when the proximal lymphatics are choked off and obstructed by existing metastasis. Therefore, it becomes necessary for us to re-investigate the zone of upward spread or to apply our existing information in this respect. We have chosen to extend our point of superior mesenteric ligation in a cephalad direction. In so doing we hope to remove an additional 2 or even 3 inches of the inferior mesenteric vessels and their accompanying lymph nodes. We feel that some metastatic nodes will thus be left on the specimen instead of in the patient. The wisdom and practicability of the manner in which this has been done awaits further study. However, we recommend that others initiate a similar clinical study.

6. We recommend that **measured ligations of the inferior mesenteric** vessels be performed as has been outlined. All of these measurements have been useful in our own investigations, and they merit further consideration.

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PRACTICAL APPLICATIONS OF Bacteriologic Studies in the Diagnosis of Infectious Diseases

SAMUEL SASLAW*

GEORGETOWN UNIVERSITY MEDICAL CENTER, WASHINGTON, D. C.

The response of the human body to various infections may be characterized by a wide variety of clinical signs, symptoms, or syndromes. With the development of efficient and specific chemotherapeutic and antibiotic agents, it has become apparent that accurate diagnosis is of considerable importance if optimum results are to be attained. However great one's clinical experience may be, he must frequently depend upon the bacteriologic laboratory to ascertain the specific etiologic agent. Once the diagnosis is established, the assistance of a good laboratory is invaluable in establishing a therapeutic regimen offering the maximal benefit to the patient in health, time, and economy. The injudicial and indiscriminate use of therapeutic agents is to be deplored as greatly in the treatment of an infectious disease as is for example the use of shotgun preparations in an undetermined anemia.

In order to receive the most information from the diagnostic laboratory it is necessary that a high degree of cooperation exists between the clinician and the bacteriologist. Unfortunately, the type of highly specialized well-appointed bacteriologic laboratories present in leading hospitals and medical centers frequently is not immediately available to the average physician practicing in the less concentrated areas of the United States. Thus it is often necessary for the general practitioner to "shop around" in order to determine and employ the most adequate and reliable facilities available and also to call upon the excellent state and federal agencies for assistance in any of the more specialized procedures.

It is not the purpose of this paper to present an exhaustive review of procedures but to emphasize the role of the clinician in obtaining the proper material necessary for diagnosis of the more common infectious diseases. Too frequently the collection and delivery of specimens are treated so carelessly and haphazardly that the laboratory is actually wasting its time in going through the motions of performing the requested examinations. The responsibility for the proper collection of materials rests with the clinician.

BACTERIOLOGIC PROCEDURES

Smears—The bacteriologic smear provides a simple tool which requires a minimum of equipment and may offer some valuable information. Although it is not to be implied that this procedure should be substituted for cultural methods, it is of value in certain instances in helping to establish a presumptive diagnosis and working hypothesis in treatment pending the results of the laboratory and can be conducted as an office procedure. In the following situations the smear is of considerable value:

1. *Throat smears*—Vincent's infection represents one of the few instances in which the sole laboratory diagnosis rests upon the smear. Speci-

*Assistant Professor of Medicine, Georgetown University School of Medicine; Acting Director, Bacteriology and Immunology Laboratories of Georgetown University Hospital and Chief of Serologic Research Section, Department of Bacteriology, Army Medical Department, Research and Graduate School, Army Medical Center, Washington, D. C.

mens are best obtained from the necrotic buccal or pharyngeal areas by firmly scraping the edges of the lesions with a stiff bacteriologic loop. When the gingivo-dental areas are involved, a bacteriologic needle is preferable. The material is then smeared directly upon a dry clean slide, fixed by passing through a flame and stained with 1 per cent methylene blue for 10 minutes. The presence of numerous spirochetes and fusiform bacilli is confirmatory.

In a similar manner yeast cells when noted in smears of creamy thrush lesions suggest a *Candida albicans* infection which should be confirmed culturally. In other infections of the throat, smears are frequently unreliable and cultures should be depended upon for definitive diagnosis. However, when diphtheria is suspected clinically and the presence of organisms morphologically characteristic of the diphtheria bacillus is noted therapy should not await cultural proof.

2. *Pulmonary infections*—The gross and microscopic appearance of sputum may be of considerable aid in certain infections. A blood-tinged sputum may be profitably examined for the possibility of tuberculosis or a bacterial pneumonia. In tuberculosis a specimen collected over a 24-hour period is preferable but under certain circumstances a morning specimen will suffice. Although the identity of acid-fast organisms should be confirmed by culture to determine whether or not they are tubercle bacilli, the clinician has obtained some presumptive evidence to support any clinical or x-ray evidence of this possibility.

The presence of a preponderance of Gram-positive cocci in a rusty sputum can suggest a bacterial pneumonia but the definitive diagnosis must usually depend on culture since the morphologic characteristics and arrangement of the pneumococci, streptococci, and staphylococci in sputum unfortunately do not always conform to the classical textbook descriptions. Direct typing of the sputum with antipneumococcus serum, however, may frequently confirm the diagnosis of a pneumococcal pneumonia. Similarly a preponderance of Gram-negative rods may suggest Friedlander's or *Hemophilus influenzae* infection.

3. *Serous cavity infections*—Frequently direct gross and microscopic examination of centrifuged specimens of spinal, pericardial, pleural, peritoneal, and synovial fluids may be of considerable assistance in determining the type of infection. In meningitis direct smears of the spinal fluid are of utmost importance. Stained sediments should be examined carefully for the organisms which commonly cause meningitis. The Gram-positive cocci can usually be found, but in a purulent fluid from a meningococcic infection the Gram-negative diplococci may be difficult to detect due to debris, cells, or autolysis. In our experience a purulent spinal fluid in which careful search fails to reveal organisms can usually be suspected of being meningococcic in origin pending cultural verification.

The detection of *H. influenzae* may also be difficult and due to their pleomorphic nature they may readily be confused with meningococci. A simple stain using either safranine or methylene blue for 5 minutes may bring out the morphologic details which can vary from rod to coccal forms more clearly. Group B influenzae bacilli may be identified serologically directly from the spinal fluid by the quellung reaction.

Smears for the detection of acid-fast bacilli in spinal fluid are negative in a high percentage of cases. The smear should be made from the pellicle if one is present and a prolonged search made.

The diagnosis of a cryptococcic (Torula) meningitis can frequently be made by smear. The yeasts are not to be confused with blood cells. When such organisms are suspected from the first observation, a drop of fluid is mixed with a drop of India ink and smeared but not fixed. The presence of encapsulated yeasts, particularly when budding forms are noted, makes the diagnosis relatively easy.

4. *Urethral smears*—The presence of Gram-negative intracellular diplococci in the male urethral discharge can usually be construed as evidence of gonorrhea. In the female, however, the diagnosis of the infection on the basis of the smear alone is of questionable value unless frank pus is seen. Nevertheless confirmation must be obtained by culture.

Cultures—The various materials obtained for culture purposes should be selected after due consideration of the results anticipated and dispatched to the laboratory as soon as possible.

1. *Blood cultures*—One of the most widely applied and useful technics in infectious processes is the blood culture. It not only serves in arriving at a precise diagnosis but also offers

a means of measuring the sensitivity of the agent to antibiotics and affords an excellent tool in following the progress of therapy. In our experience several blood cultures begun at 30 to 60-minute intervals 2 to 3 hours before the peak of the temperature curve are preferable to single daily cultures. Much time can be saved when the media show early growth while if no growth has occurred, cultures can be repeated on subsequent days. One must consider the transient nature of a bacteremia wherein the respective agents may be present only in certain stages of the disease. For example a culture taken early in the course of a bacterial pneumonia or meningococcemia can yield valuable information but may be negative at a later interval.

In a hospital where technicians are available at all times we prefer to inoculate the suitable liquid media at the bedside in addition to collecting blood in a citrated tube from which agar pour plates may be prepared. However, the entire specimen may be introduced into a citrated tube and then taken immediately to the laboratory for inoculation of the respective media.

For routine cultures 100 ml. quantities of beef infusion and thioglycollate broths are each inoculated with 5 ml. of blood. The latter medium will support the growth of most anaerobes. If incubation facilities are not immediately available the cultures should be refrigerated. Best results are obtained if the laboratory is informed concerning the possible nature of the infection so that special procedures may be employed where indicated, as in brucellosis and tularemia. Also notation should be made if the patient has received any sulfonamides or antibiotics so that available neutralizing agents may be employed.

2. *Bone marrow*—Occasionally cultures of the bone marrow usually obtained by sternal aspiration may aid considerably in securing a bacteriologic diagnosis when blood cultures are negative. We have successfully isolated such agents as *Mycobacterium tuberculosis, Brucella, Histoplasma,* and *Actinomyces* from the marrow. The aspirated material is inoculated directly into the media required to grow the suspected agent.

3. *Eye, ear, nose, and throat*—Particular care must be observed if the taking of throat cultures is to pay dividends. First of all properly prepared, tightly bound swabs are essential. Precautions must be taken to avoid contamination from saliva and adjacent areas. With the tongue depressed the swab is rolled firmly over the involved area. To avoid receiving dried swabs which are unsatisfactory it is preferable to place the swab into a tube containing 1 ml. of infusion broth and twirling it gently to distribute the organisms. Saline is not recommended since it is toxic for some organisms. If a delay is expected in transit to the laboratory, the material is refrigerated to prevent death or overgrowth of the significant organisms. This procedure can be followed for culture of the eye, ear, and nose as well.

Cultures from infants are more readily secured with a nasopharyngeal swab consisting of tightly-wound cotton on a soft flexible wire which is inserted through the nostril into the nasopharynx. This technic is particularly useful in pertussis and also as a substitute for a sputum specimen in an infant with pneumonia.

4. *Bile*—At times it is practicable to examine bile from patients with cholecystitis or to seek the typhoid bacillus in suspected carriers. The bile is obtained with a duodenal tube by fractions which are kept separate from the first intestinal portions or directly during surgery. Anaerobic and aerobic cultures are indicated.

5. *Sputum*—For the diagnosis of acute or chronic respiratory infections, sputum specimens are most satisfactory when obtained after the patient awakes and has brushed his teeth. He should then attempt to produce sputum by coughing up the material and expectorating into a sterile container. In infants and children it is usually necessary to induce a cough by tickling the pharynx and to collect the sputum on a swab. In suspected tuberculosis a 24-hour specimen is preferable.

With sputum collected for the diagnosis of suspected fungus infections such as coccidioidomycosis, histoplasmosis, blastomycosis, and moniliasis the addition of 20 units of penicillin and 40 units of streptomycin each per milliliter of sputum inhibits the bacteria but not fungi, except for *Actinomyces*. This procedure is particularly of value with gastric washings or when specimens are not immediately cultured.

Caution must be observed in interpreting the significance of the presence of such fungi as *Monilia* or *Aspergillus* as the cause of primary lung infections. Repeated cultures ought to be obtained and in the case of *Monilia* the laboratory should be requested to determine the po-

tential pathogenicity of this agent by mouse inoculation and the ability to form chlamydospores on corn meal agar. When lung abscess is suspected anaerobic cultures are particularly indicated in addition to the usual aerobic procedures as well as smears for fusospirochetosis.

When gastric washings are obtained the entire specimen should be submitted to the laboratory. If any delay is anticipated, in addition to refrigeration, it is advisable to add enough 20 per cent sodium hydroxide to render the contents approximately neutral.

6. *Feces*—Whenever laboratory facilities are immediately available, collection of stool specimens by the rectal swab is preferable. The cotton-wrapped tip of an applicator stick is placed into a 1½-inch hard rubber sleeve which is beveled at the distal end and then sterilized. Prior to use the periphery, but not the end, of the rubber is lubricated and inserted into the rectum. The applicator is then pushed forward and the mucosa swabbed in a firm circular motion. Thereupon the applicator is drawn back into the sleeve, the apparatus removed, and placed into a sterile test tube for immediate delivery to the laboratory which should be informed of the suspected diagnosis.

When a whole stool specimen is to be submitted instead of the swab, a soft stool is preferable to a solid one. If there is no diarrhea and catharsis is not contraindicated, a specimen may be so obtained in a clean container. When immediate examination is not anticipated, 1 to 2 gm. of feces should be placed in 30 per cent glycerin in an alkaline buffered salt solution (*p*H 7.6) at a ratio of about 1 part feces to 10 of glycerin. However, it can not be too greatly emphasized that immediate examination of stools offers a far greater yield of significant results.

7. *Urine*—Catheterized specimens for all urine cultures are recommended and are mandatory in females. If special care is taken a noncatheterized specimen in males may offer satisfactory results. In the latter instance the glans and meatus are carefully washed with soap and water. Then the intermittent method of voiding is employed in which the first portion of the specimen is discarded and the remainder collected in a sterile container. It is our practice to inoculate all isolates on urea agar to determine whether or not the organism is a urea splitter. The potential role of such organisms in contributing to or causing nephrolithiasis can not be overemphasized.

8. *Urethral and prostatic cultures*—The most frequent examination requested of urethral or prostatic material is for the presence of *Neisseria gonorrhoeae*. In the male with an acute infection at least 2 swabs are taken of the pus expressed by gentle pressure. The first swab is designated for culture where more material is required while the second can be used for smear. An early morning urine is likewise desirable for examination and may yield results as good as the swab method in the acute cases. In chronic infections urine and prostatic fluid are collected in sterile containers.

In the female, specimens are taken from the urethra and cervix and from vaginal secretions when vulvovaginitis is present. Whenever possible the material should be inoculated promptly. If a delay is anticipated the swabs are placed in a sterile tube containing 1 ml. of proteose peptone broth No. 3 and refrigerated immediately. Although organisms may be recovered after 6 to 8 hours of refrigeration, the results are not as satisfactory as those obtained after immediate inoculation. Standing at room temperature will result in a rapid deterioration of the specimen's value. Urine should likewise be refrigerated when immediate study is to be delayed.

9. *Vaginal and uterine cultures*—Before specimens are procured, one must be sure that douches or antiseptic vaginal creams or jellies have not been used during the previous 3 to 4 hours. Any residue of such materials should be washed away and plain sterile vaseline used on the speculum instead of antiseptic lubricants which can inhibit certain organisms. Sterile swabs used to collect pus from the urethra, Bartholin glands, vagina, or cervix are treated as described above.

10. *Spinal fluid*—In suspected meningitis a lumbar puncture is indicated as soon as possible. If chocolate agar slants are available it is preferable to allow the first 5 to 10 drops to fall into the tube. In addition the latter 5 ml. are collected in a sterile tube and sent along to the laboratory with the slant. When incubated under partial carbon dioxide tension, the chocolate agar will grow most of the more common bacterial agents causing meningitis. The fluid in the tube is used to inoculate the appropriate media. If tuberculous meningitis is suspected

guinea pig inoculation is indicated in addition to culture.

11. *Wounds*—The collection of material from wounds, abscesses, or sinuses requires care and judgment in selecting the type of sample most likely to yield significant results. If there is a copious amount of pus or serous material, a generous quantity should be obtained in sterile tubes or capillary pipettes. It is more preferable to allow the laboratory to discard any unused material than to send a fraction of a specimen.

Pus or exudates from smaller lesions may be obtained with swabs. However, it is often advisable to curette the walls of an abscess or sinus since old pus in the lumen of a cavity may frequently be sterile. This is of particular value in suspected actinomycosis where in addition dressings covering the sinus may also be profitably sent to the laboratory for examination and culture. Consultation with the laboratory concerning the nature of the specimen and the clinical possibilities may be amply rewarded. This is particularly true when anaerobic infections such as those of the *Actinomyces bovis* type, gas gangrene, or tetanus are suspected. Similarly tuberculosis or cutaneous diphtheria may be missed if the laboratory is not advised of these possibilities.

12. *Epidermal cultures*—In addition to bacterial infections the skin is frequently affected by fungi or yeasts. Since the recognition of fungus pathogens rests upon morphologic characteristics in the tissues as well as in culture, care should be exercised in obtaining suitable material. After cleansing the skin with alcohol and ether, scales may be obtained by scraping the surface with a dull blade or scalpel. Then the material should be placed in a sterile container or between 2 clean, previously flamed glass slides and wrapped. Specimens from nails are secured in a similar manner. When hair is involved, affected portions are cut or plucked.

Although the definitive recognition of the specific agents requires the services of a competent mycologist, the clinician can frequently determine whether or not a fungus infection is present. Skin, hair, or nail scrapings are examined after adding 10 to 20 per cent potassium hydroxide to the material on the slide, gently pressing the specimen under a cover glass and warming the slide carefully over a small flame. The preparation is then examined unstained. Branched or unbranched hyphal filaments in nail or skin scrapings and small spores within or directly surrounding the hair shafts are sufficient evidence that the agent is a fungus.

SEROLOGIC PROCEDURES

Considerable information can be obtained by the judicious application of serologic procedures. It can not be emphasized too greatly that serial specimens yield a far greater amount of information than a single sample. In most infectious diseases the peak titer is reached between the second and third weeks so that it is advisable to secure a baseline serum before the end of the first week if comparisons are to be made. Frequently serum is not obtained until late in the disease or during convalescence after the peak titer has been reached. Then the question arises as to what constitutes a "significant titer." A direct reply is often difficult and must be carefully considered in terms of the patient's history, previous immunizations, and residence as well as the particular laboratory's "normal" values. Variations in technics, antigens, and personnel can result in differences in results from one laboratory to another. Thus the laboratory should be consulted on the significance of results obtained.

1. *Agglutinations*—Agglutinations are of particular value as indirect evidence of certain infectious diseases where recovery of the organism has not been achieved. In brucellosis, for example, when isolation has not been successful, serologic studies may yield the only laboratory aid. A titer of 1:80 is usually considered significant in the ordinary population. However, in individuals previously immunized with cross-reacting cholera vaccines or in persons with high exposure rates such as veterinarians, packing house employees, butchers, farmers, and dairymen, serologic results should be carefully analyzed. A negative test does not exclude brucellosis.

The interpretation of agglutination results for typhoid or paratyphoid infections in particular must be made with due consideration of previous immunizations. The titer against the 0 (somatic) antigen is of more significance in diagnosis since following immunization, 0 agglutinins fall to a low titer in about six months and are usually absent in a year. On the other hand the H (flagellar) agglutinins may persist for several years. If serial specimens are not obtained, a single specimen taken by the seventh to tenth day of disease showing an 0 titer of 1:50 or above in a person not vaccinated during

the past year or two suggests infection. However, both in vaccinated and nonvaccinated individuals serial specimens should be obtained if possible.

In tularemia a titer of 1:80 or above is suggestive of infection. Care must be taken to rule out cross reactions with *Brucella* antibodies.

The marked variability and cross reactivity of dysentery antigens makes the use of serologic tests of no practical value in routine testing for dysentery.

2. *Antistreptolysins*—Frequently laboratories are requested to perform antistreptolysin determinations for assistance in the diagnosis of rheumatic fever. It must be emphasized that since this procedure measures the antibodies to the hemolytic toxin of the streptococcus, it is not a specific test for rheumatic fever. However, if the clinical picture suggests rheumatic fever and there is a high rising titer, the laboratory results can serve to confirm the diagnosis but a negative test does not rule it out. To state an arbitrary titer is difficult since "normal" levels may vary considerably with the locale and test employed. Thus the results must be interpreted on the basis of the individual laboratory's normal values.

3. *Virus and rickettsial infections*—For the diagnosis of rickettsial infections it is best to procure a specimen before the sixth day and at weekly intervals. These sera can first be screened in the routine laboratory by means of the Weil-Felix reaction employing OX-19, OX-2, and OX-K Proteus organisms which contain antigens common to certain rickettsial agents. A rising titer in serial specimens offers presumptive evidence of rickettsial disease. If a single specimen is obtained only a titer of over 1:160 should be considered.

The Weil-Felix test has its limitations, however, in that it is of no value in differentiating epidemic and murine typhus and frequently fails to differentiate Rocky Mountain spotted fever from the latter. Also serum from patients with Q fever and rickettsialpox do not react with the antigen while Brill's disease may frequently be missed with this test. Specific serologic results are derived by complement-fixation and agglutination tests using rickettsial antigens. These latter tests are performed by specialized laboratories.

Most laboratories routinely do serologic tests for agents presumably of virus origin such as infectious mononucleosis and primary atypical pneumonia. In the former an increased titer of agglutinins for sheep red blood cells is obtained in 50 to 80 per cent of cases. Thus a negative reaction does not rule out the disease. The presence of rising titers with levels of at least 1:80 or more is usually significant. It must be remembered that certain individuals may contain normal hemagglutinins or may have an increased titer due to the previous administration of horse serum in the form of antitoxin. Errors can be avoided if an absorption test is requested in questionable cases. Guinea pig antigens will absorb out the antibodies not due to infectious mononucleosis—i.e. normal and horse-serum induced antibodies. As an added check, boiled beef erythrocytes will absorb out the heterophile antibodies due to both infectious mononucleosis and horse serum.

In primary atypical pneumonia two serologic tests may be employed for laboratory diagnosis—the cold hemagglutination and the streptococcus MG agglutination tests. In the former the patient's serum when positive will agglutinate human group 0 erythrocytes at 0 to 10° C. but the reaction disappears at 37° C. The maximum titer is obtained between the second and fourth week after the onset of illness and on the average about 55 per cent of cases will yield positive results. In mild illnesses only about 20 per cent may be positive while in severe or prolonged disease as high as 90 per cent are positive.

Blood collected for this procedure should not be placed in the refrigerator before the serum is removed since homologous red cells will absorb some of the antibody. The blood should be warmed to 37° C. before removal of the serum in order to free any antibody which may have combined with the red cells of the patient. A fourfold increase in titer is usually significant but if only a single specimen has been obtained a titer of 1:32 or higher is abnormal. Increased cold agglutinins may also appear in such varied instances as mumps, orchitis, hemolytic anemias, malaria, and hepatic disease which are not readily confused clinically. Antibodies against the streptococcus MG may occur in 20 to 75 per cent of cases in abnormal titers of 1:20 or higher. In our experience we have found no particular advantage in using both tests and if one is to be used, cold hemagglutinins would be our choice.

Serial specimens when properly collected and submitted to specialized laboratories can assist in the diagnosis of the more common virus diseases such as influenza, psittacosis, lymphogranuloma venereum, mumps, and the encephalitides. Virus isolation is a very specialized procedure and requires materials which most laboratories do not have. When such studies are indicated the cooperation of a virus laboratory should be sought.

3. *Mycotic infections*—Relatively few of the systemic mycoses lend themselves to serologic evaluation. Serologic tests for coccidioidomycosis, blastomycosis, and histoplasmosis have been demonstrated to be of practical value. Relatively few institutions, such as the Army Medical School and the National Institutes of Health, are set up to do all 3 tests. The skin test with coccidioidin, blastomycin, and histoplasmin must be interpreted in the same manner as tuberculin tests. Complement-fixation tests in coccidioidomycosis and blastomycosis are positive in patients with severe infections and are highest when dissemination occurs, but may be absent in mild cases. Preliminary studies with histoplasmosis suggest that high titers may be obtained early in the disease but may drop off to insignificant levels in convalescence or in chronic cases and may be negative in fulminating disease.

ANTIBIOTIC THERAPY

The results of in vitro bacterial sensitivities to antibiotics afford an opportunity for calculating the estimated dosage required in treatment. In general the following working hypothesis may be employed. For every 100,000 units of penicillin given over a 24-hour period, a blood level of 0.1 unit per milliliter may be anticipated. In bacterial endocarditis where a bactericidal concentration is desired it is advisable to obtain 5 to 10 times the estimated inhibitory level. For example with an organism sensitive in vitro to 0.2 unit per milliliter, a blood level of 1 to 2 units per milliliter can be expected with a daily dose of 1 to 2 million units.

With streptomycin the average blood level 3 hours after injection is about 2 to 3 micrograms for each 0.1 gm. administered. Doses of 0.5 gm. at 6-hour intervals can be expected to maintain a high concentration while lesser doses may be more effective at 3 to 4-hour intervals.

Oral doses of chloromycetin and aureomycin yield blood levels of approximately 2 to 8 micrograms per gram of drug.

The above data represent average estimations and may vary in individual cases. The clinical response and assays of body fluids are a more definitive measure of the therapeutic effects.

SUMMARY

No pretense has been made to present a comprehensive review of bacteriologic applications in infectious diseases. More detailed information may be obtained from the references given.

With the "Golden Age" of antibiotics rapidly advancing it is evident that the identification of infectious agents is not purely an academic procedure. It is even more important that a close liaison be maintained with the bacteriology laboratory so that with the advent of more and more specific therapeutic agents, the clinician will be prepared to derive the greatest benefit in the precise diagnosis and treatment of infectious diseases.

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Diagnosis and Treatment of Acute Pancreatic Disease

ROBERT J. COFFEY,[1] EARL B. BARNES,[2] PAUL REED[3] AND FREDERICK B. BRANDT[4]

GEORGETOWN UNIVERSITY SCHOOL OF MEDICINE, WASHINGTON, D. C.

Formerly believed to be of relatively rare clinical occurrence, acute pancreatic disease has in recent years become recognized as a common abdominal disorder. Fewer cases escape recognition today, principally because of an increased awareness of this condition as a cause of acute upper abdominal pain plus the more frequent use of the serum amylase determination. During the period of 1947 to 1949 we have personally observed 90 cases of acute pancreatitis at Georgetown University Hospital and its affiliated institutions. In contrast, only 27 cases of acute pancreatic disease were observed in these same institutions during the period of 1937 to 1939, although the total number of admissions had not changed significantly.

FORMS OF ACUTE PANCREATIC DISEASE

There are two distinct forms of acute pancreatic disease: (1) *acute edematous pancreatitis,* a self-limited condition characterized by upper abdominal pain of 3 to 6 days' duration, an absence of shock, and an elevation of the serum amylase, and (2) *acute necrotic pancreatitis,* a highly lethal disease in which the upper abdominal symptoms are usually associated with shock and with the eventual death of the victim or suppuration of the pancreas with a collection in the lesser sac. Regardless of whether these two conditions refer to different phases of the same disease process, or whether they are two distinct clinical entities, the fact remains that they are recognizably different on the basis of both pathologic and clinical features, and are reproduced in experimental animals by different means.

In this series 54 cases were classified as acute edematous pancreatitis whereas in 36 cases a necrotic form of the disease was identified. Twenty-three cases of chronic pancreatitis were encountered in this same review. The sex distribution is interesting in that the edematous variety occurs with greater frequency in females (32 females to 22 males), while acute necrotic pancreatitis was encountered more frequently in males (29 males to 7 females).

Because of the very low mortality associated with acute edematous pancreatitis, opportunity for histopathologic study of the pancreas in this condition is infrequent. Grossly, the pancreas is firm and swollen and regional fat necrosis may or may not be present. In the necrotic variety, on the other hand, the pancreas is, in the early stage, characteristically hemorrhagic, following which necrosis and suppuration ensue. The tendency to hemorrhage is seen not only in the pancreas, but is also manifested by the presence of free bloody peritoneal fluid as well as subserosal and retroperitoneal extravasations of blood.

What, then, is the essential distinction between the edematous and necrotic forms of acute pancreatitis? There is convincing evidence, based on both experimental and clinical studies, that the all-important difference is the intrapan-

[1]Professor of Surgery, Georgetown University School of Medicine, Washington, D. C.

[2]Instructor in Surgery, Georgetown University School of Medicine, Washington, D. C.

[3]Adjunct Instructor in Surgery, Georgetown University School of Medicine, Washington, D. C.

[4]Assistant Chief, Surgical Service, Mt. Alto Veterans Hospital.

creatic activation of the enzyme "trypsinogen" in necrotic pancreatitis, a process that does not occur in the edematous form of the disease. This conversion of the innocuous trypsinogen into the highly potent trypsin normally takes place in the duodenum as the result of the action of enterokinase. The release of active trypsin within the pancreas itself has been shown experimentally to reproduce the hemorrhage and necrosis observed in clinical forms of acute necrotic pancreatitis.[1,2]

ETIOLOGIC FACTORS

In both the diagnosis and treatment of acute pancreatitis familiarity with the known and suspected etiologic factors is desirable. For many years investigators have interested themselves in the experimental production of acute pancreatitis, and many theories have been expounded. The long-popularized concept of Opie[3] that a gallstone impacted at the ampulla of Vater, converting the common bile duct and major pancreatic duct into a common channel, permitted reflux of bile into the pancreas and thus converted trypsinogen to trypsin, has not been substantiated. In the first place, such impacted stones at the ampulla are rarely encountered, and in addition, one of us (R. J. C.)[4] was unable to demonstrate the trypsinogen-converting capacity of bile. Archibald postulated the idea that a similar common channel was established, as the result of associated gallbladder or duodenal disease, by spasm of the sphincter of Oddi.

In attempts to reproduce acute pancreatitis experimentally by one of us (R. J. C.),[4] the only successful method consisted of ligation or evulsion of the pancreatic ducts plus physiologic stimulation of the pancreas with pilocarpine. We believe, therefore, that ductal obstruction of the pancreas, followed by physiologic stimulation of the exocrine secretion, results in stasis and increased pressure within the pancreas with rupture of the finer ductules, and escape of the pancreatic juice, with its contained trypsinogen, into the parenchyma of the gland. It has been shown experimentally that this released trypsinogen may be converted into trypsin by the action of tissue juices, bacteria normally present in the pancreatic ducts, calcium, and the enzymes contained in erythrocytes and leukocytes. In these same experimental studies it has been observed that edematous changes in the pancreas may be produced by a great variety of means, including trauma of the gland or obstruction of the ducts.

In a consideration of the clinically indicted etiologic factors, impressive correlation with the aforementioned experimental studies is evident (Table 1). The association of acute pancreatic disease with *alcoholism* is well known, and was observed in approximately one-half of the cases in this series. Usually these individuals are chronic alcoholics but not infrequently acute pancreatitis occurs after a single debauch in an otherwise moderate individual. The etiologic role played by alcohol probably stems from its production of duodenitis, resulting in congestion of the duodenal mucosa with obstruction of both the Vaterian and minor duct papillae. Moreover, the obstructing metaplasia of the epithelium of the pancreatic ducts observed by Rich and Duff[2] may well be a part of the vitamin deficiency so often associated with chronic alcoholism.

Associated *gallbladder disease* was identified in an impressive number of these cases. Its association with the edematous form of pancreatitis is more common, and it has been theorized that extension of infection through the rich intercommunicating lymphatics between the biliary system and the pancreas probably occurs. Spasm of the sphincter of Oddi in biliary tract disease may also play a role.

Trauma is an important etiologic factor more often than is generally thought (Table 2). In the 10 cases directly related to trauma the injury was inflicted at the time of surgery in 5. In 2

TABLE 1

PROBABLE ETIOLOGIC FACTORS IN ACUTE PANCREATITIS

	ALCOHOLISM, PER CENT	GALLBLADDER DISEASE, PER CENT	TRAUMA, PER CENT	INTESTINAL OBSTRUCTION, PER CENT	COMMON DUCT STONE, PER CENT
Edematous	40	31.5 (18.5)*	13	5.5	1.8
Necrotic	50	11	11	2.8	2.8

*Demonstrated at operation.

cases epigastric pain with an elevation in serum amylase followed immediately after visualization of the common duct with diodrast injected through a T-tube. In both these instances the reflux of the diodrast into the major pancreatic duct was demonstrable by x-ray (Figure 1).

Of the 4 cases in which *intestinal obstruction* was associated with acute pancreatitis, a strangulated femoral hernia was found in 1, gangrene of the ileum as a result of volvulus in another, and in 2, obstructing postoperative adhesions were present. In our opinion, if a true causal relationship between intestinal obstruction and acute pancreatitis exists, it can be explained only on the basis of increased intraintestinal pressure, resulting finally in increased intraduodenal pressure and stasis within the pancreatic ducts. In only 2.8 per cent of the cases of necrotic pancreatitis and in 1.8 per cent of the edematous variety was a *common duct stone* encountered.

DIAGNOSIS

It is our firm conviction that in all cases of acute upper abdominal pain the diagnosis of acute pancreatic disease must be excluded by the routine determination of the serum amylase level. Little additional information results from the urinary diastase determination. The value of a serum lipase level is limited in acute pancreatic disease because of the time involved in this determination. Recent studies in our laboratory indicate the determination of the antitryptic activity of the blood in acute pancreatic disease may be useful in differentiating the acute necrotic from the acute edematous type.[5]

In distinguishing acute edematous pancreatitis from the necrotic form certain clinical features are distinctive (Table 3). Edematous pancreatitis was associated, in this series, with no mortality, whereas in acute necrotic pancreatitis the patients were profoundly ill, and the associated mortality was 88 per cent. In the edematous form recurrent attacks were common and often eventuated in chronic relapsing pancreatitis. In edematous pancreatitis the average duration of symptoms was 6.2 days with complete recovery, whereas in acute necrotic pancreatitis the majority of cases expired during the first week of the illness, and those who survived did so only after a stormy period of approximately 3 weeks. These survivors frequently developed suppurative collections in the lesser omental sac.

The effect of the acute inflammation of the pancreas on the adjacent celiac ganglia, and perhaps of the intraperitoneal escape of pancreatic juices, was evidenced by the occurrence of paralytic ileus in approximately one-fourth of these cases. Upper abdominal distention associated with hypoactive or absent peristalsis was the usual finding. Roentgenograms of the abdomen frequently revealed dilated loops of bowel with fluid levels, often suggesting an erroneous diagnosis of intestinal obstruction.

Jaundice, while occurring in both forms of the disease, was seen more frequently and in a more pronounced form in the necrotic variety. Derangements of carbohydrate metabolism, as evidenced by glycosuria or hyperglycemia, occurred less often in the edematous form of the disease and were usually transitory. On the other hand, in one-half of the survivors of necrotic pancreatitis the diabetes was permanent and moderately severe.

THE *sine qua non* of diagnosis is the serum amylase determination. After having reviewed all serum amylase determinations carried out by our laboratories, it is our conclusion that, except in cases of epidemic parotitis and perforated peptic ulcer, an elevation of the serum amylase is absolutely diagnostic of pancreatic disease. However, the degree of serum amylase

TABLE 2

CASES OF TRAUMATIC PANCREATITIS

	EDEMATOUS	NECROTIC
1. Following nonpenetrating trauma of abdomen	1	1
2. Following penetrating wounds of abdomen		1
3. Following surgical trauma		
Transduodenal exploration of ampulla of Vater		1
Gastrectomy for duodenal ulcer	2	
Cholecystectomy and manipulation of pancreas	1	
Biopsy of edematous pancreas		1
4. Following cholangiography	2	

FIGURE 1. Cholangiogram in which reflex of diodrast (35 per cent) into the major pancreatic duct was followed by acute abdominal pain and an elevation of serum amylase.

elevation provides no help in distinguishing edematous from necrotic pancreatitis. In fact, we found that the average elevation, as determined by the Somogyi method, is slightly higher in the edematous form. In many cases serial serum amylase determinations were carried out, but we were unable to recognize any characteristic pattern. In both forms of acute pancreatitis the elevation may be transitory or sustained.

It has been observed in several cases of necrotic pancreatitis that a sustained elevation is frequently associated with a collection in the lesser omental sac, drainage of which is followed promptly by a return to normal (Figure 2).

TABLE 3

DISTINCTIVE FEATURES OF EDEMATOUS AND NECROTIC PANCREATITIS

	EDEMATOUS	NECROTIC
1. Mortality	0	88 per cent
2. Previous similar episode	13 per cent	8.3 per cent
3. Subsequent similar episode	28.5 per cent	0
4. Average duration of symptoms	6.2 days	4.2 days (fatal cases) 21 days (survivors)
5. Lesser sac collections	0	16.6 per cent
6. Paralytic ileus (roentgen)	24 per cent	28 per cent
7. Jaundice	11 per cent	20 per cent
(average icteric index)	18	76
8. Glycosuria or hyperglycemia	11 per cent	27.7 per cent
9. Average serum amylase (Somogyi units)	836	721

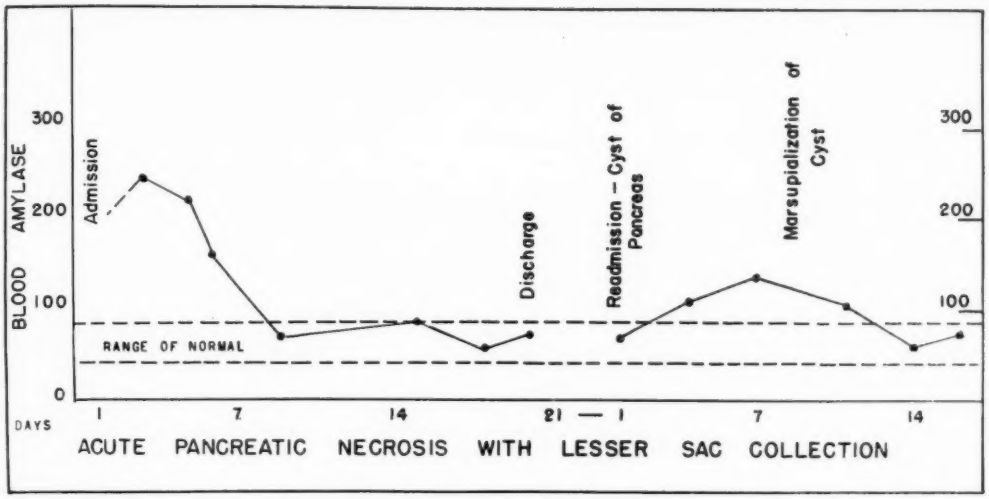

FIGURE 2. Elevation of serum amylase on readmission due to necrotic collection in lesser omental sac.

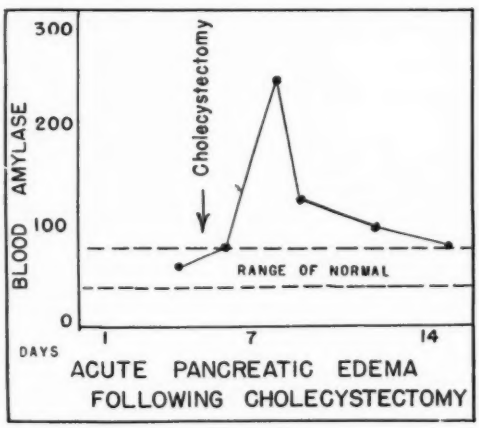

FIGURE 3. Post-cholecystectomy elevation of serum amylase.

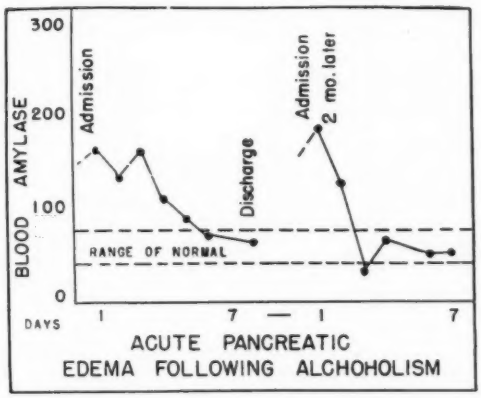

FIGURE 4. Serum amylase elevations in recurrent edematous pancreatitis.

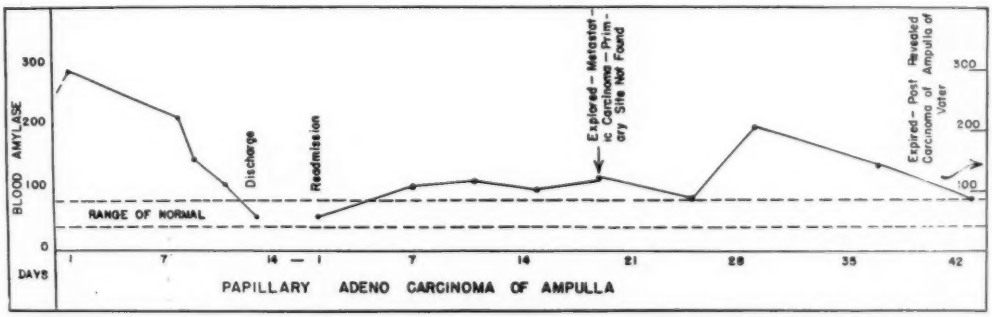

FIGURE 5. Serial serum amylase levels in case of papillary adenocarcinoma of the ampulla of Vater.

TABLE 4
CONSERVATIVE TREATMENT

EDEMATOUS	NECROTIC
1. Pain relief	1. Pain relief—splanchnic block
2. Nothing per os	2. Nothing per os
3. Barbiturates	3. Wangensteen suction
4. Wangensteen suction	4. Barbiturates
5. Interval cholecystogram	5. Blood and substitutes
6. Avoidance of alcohol	6. Penicillin
7. Avoidance of dietary indiscretion	

TABLE 5
INTERVAL SURGICAL TREATMENT

EDEMATOUS	NECROTIC
1. Interval cholecystectomy for demonstrable disease, 7 cases (no recurrence in 5)	1. Early operative interference discouraged
2. Interval common duct exploration in cases with jaundice, 5 cases (calculus found in 3)	2. Aspiration lesser sac collections, 2 cases
	3. Marsupialization of lesser sac collections, 2 cases

Following surgical trauma, i.e. cholecystectomy with manipulation of the pancreas, a transitory rise occasionally occurs (Figure 3). Each recurrence of pancreatic edema is usually associated with a rise in the serum amylase level (Figure 4). Similar elevations have been observed in association with other lesions causing obstruction of the pancreatic ducts (Figure 5).

TREATMENT

As a result of inadvertent or designed surgical interference in cases of acute pancreatitis, we have become convinced that the victim's welfare is best protected by conservative, nonoperative measures during the acute stage of the disease (Table 4). In both forms of acute pancreatitis the logical principles of treatment are (1) physiologic splinting of the pancreas, and (2) promotion of pancreatic drainage.

In the *edematous* variety the treatment is largely symptomatic. Relief of pain is best obtained by the use of demerol which is doubly effective because of its atropine-like side effect. Physiologic rest of the pancreas is best secured by withdrawal of all fluid and food by mouth plus Wangensteen drainage through an indwelling stomach tube. Barbiturates have been shown in our laboratory to effectively suppress pancreatic secretion.[6] Following recovery from one attack of acute edematous pancreatitis, avoidance of alcohol and dietary indiscretions is mandatory.

TABLE 6
RESULTS OF SURGICAL VERSUS CONSERVATIVE MANAGEMENT

PROCEDURE	NUMBER OF CASES	MORTALITY, PER CENT
Laparotomy	9	88 (1 survival)
Choledochostomy	2	100
Release of obstructing band	1	100
Drainage of pancreas or lesser sac	4	100
Early surgery		97
Nonsurgical treatment		73.9
Delayed surgery (aspiration and marsupialization of collections)	4	0

In *necrotic* pancreatitis relief of pain is usually a more difficult problem, often requiring novocain injection of the splanchnic nerves. However, we have not observed the dramatic improvement in the clinical status of the patient observed by Gage and Floyd[7] following this procedure. Prostration and shock, as well as evidence of blood loss as manifested by a progressive fall in the hematocrit, require the use of blood or its substitutes. Since suppuration not infrequently occurs in the necrotic form, penicillin or other antibiotic therapy is indicated.

In both forms of acute pancreatitis surgical measures may be indicated after subsidence of the acute attack (Table 5). In the edematous form interval cholecystectomy for demonstrable gallbladder disease is indicated. In 7 cases of this series there has been no recurrence of edematous pancreatitis in 5 cases following cholecystectomy. In 5 cases in which jaundice was associated with or persisted after an attack of acute edematous pancreatitis, delayed exploration of the common duct led to the identification and removal of calculi in 3 cases.

In necrotic pancreatitis early operative interference only shocks an already shocked patient. Subsequent drainage of lesser sac accumulations may be required. Two cases in which the lesser sac accumulation was aspirated required subsequent drainage by marsupialization. An analysis of our experiences with the surgical versus conservative treatment is shown in Table 6.

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Some Problems Presented by Cranial Defects

O. HUGH FULCHER[1] AND ARTHUR A. MORRIS[2]

GEORGETOWN UNIVERSITY MEDICAL CENTER, WASHINGTON, D. C.

PATIENTS suffering with cranial defects have previously constituted a neglected group, due partly to the lack of a uniformly successful therapy. Furthermore, the interests of the surgeons have been frequently so concentrated on the underlying brain that they have given little thought to the bony covering. They may often have been unfair to those who persistently sought treatment by concluding that they were probably suffering with neuroses. Since there have been great advances in neurophysiology during the past decade the problems presented by cranial defects have demanded attention. Numerous individuals with cranial defects have been studied by many physicians who have reported that they do exhibit symptoms that comply with a definite pattern and that they are almost invariably relieved by successful cranioplasties.

Interest in cranial defects was greatly stimulated during the first world war. The "defect syndrome" was described and emphasized by Kerr. He stated that patients who had skull defects were morose, retiring, and would avoid their fellows; they would frequently have headaches and would be irritated by loud noises. He further stated that exposure to the sun would often cause headaches and prostration, and that stooping over or any sudden change in position would often produce dizziness. He thought that the fear of injury and the knowledge of the incomplete protection to the brain probably contributed to the characteristic train of symptoms. He emphasized that there did exist a definite disability from skull defects and that this disability was independent of any accompanying neurologic lesion. He concluded that the "defect syndrome" could be cured by a successful repair.

At that time Kerr pointed out the various methods of repair but he preferred the cranial osteoperiosteal graft. He thought that the operation should be delayed for at least 3 months following the healing of the wound or even longer if infection had existed. He stated that when the cranial defect had been successfully repaired the patients became bright, active men who resumed their places among their fellow soldiers and attacked the problem of re-education with hopeful vigor. They did not suffer from dizziness. The headaches disappeared and they were no longer sensitive to loud noises and the heat of the sun. Kerr concluded that all cranial defects should be repaired—a concept in advance of the time (1919).

Schoenfeld, who had an extensive experience with the cranial osteoperiosteal graft, was likewise impressed by the relief of symptoms effected by the successful cranioplasty. He stated, however, that frequently the osteoperiosteal graft would not restore the normal contour of the skull but simulated a healed depressed fracture.

Grant and Norcross contributed their classical article on the eve of renewed interest in the use of alloplastic materials. They recorded that the first efforts were made by van Meekren in 1670 who used the bone of a dog with apparent success. Merrem in 1810 experimented with dogs and von Walther in 1821 did a cranioplasty on man. The development of aseptic surgical technic and Olliers' work on heterogenous bone grafting constituted a background for renewed efforts. During the 1870's attempts were made at cranial repair with osseous buttons and decalcified bone. In 1889 Seydel used an osteoperiosteal graft from the tibia which he

[1]Professor of Neurosurgery, Georgetown University Medical Center, Washington, D. C.

[2]Instructor in Neurosurgery, Georgetown University Medical Center, Washington, D. C.

reduced to small pieces and placed in the defect. Various surgeons made use of heterogenous bone grafting for repairing cranial defects from 1870 to 1890. In 1890 Mueller used the flap of scalp, the pericranium, and the outer table of the skull for this procedure.

In 1891 Hinterstoisser used celloid successfully—the first record of the use of alloplastic material during the modern surgical era. In 1939 Ney reported 300 cases of cranioplasties with celloid resulting in only 5 infections. He reoperated successfully on 4 of these patients after an interval of 6 months.

From 1891 to 1903 no new method for cranioplasties was introduced. In 1903 von Hacker did the first osteoperiosteal cranial graft, which method enjoyed great popularity during the ensuing decade. From 1909 to 1915 the osteoperiosteal graft from the tibia became the most popular method of cranial repair. Delageniere reported 104 cases with only 2 failures; 1 of these was subsequently reoperated successfully.

Morestin used cartilage in 1915, Westermann used sternum in 1916, and Villandre reported the use of bone soup during the same period. Sicard, Dambrin, and Roger reported the use of treated cadaver skull in 1918. Kreider in 1920 used autogenous bones removed from comminuted fractures of the skull which he had preserved by burying them subcutaneously in the abdomen. MacLennen in 1920 used the scapula because it had periosteum on both sides. Pickerill used ilium in 1921.

Grant and Norcross reported 89 operations on 83 patients performed between 1911 and 1938 using various methods of cranioplasty. They secured adequate follow-ups on 58 patients whose defects had been repaired by osteoperiosteal cranial transplant. There were only 3 failures. The most frequent symptom of these patients suffering with cranial defects was convulsive attacks which occurred in 27 individuals of whom 18 were cured. Seven of 8 patients in their series were cured of cosmetic complaints, 2 of 2 were cured of pulsations, and 7 of 10 were relieved of headache. Eleven had weakness and paralysis of whom 6 were improved. Their results indicated that the correction of a cranial defect represented a successful surgical procedure.

The disadvantage of the autogenous osseous method of repair was that a long convalescence after the original injury was necessary and another long period of time after the operation was required before the graft would become firm. Many surgeons had made efforts to use various metals that might shorten convalescence. Aluminum was used in 1893 by Booth and Curtis and later by Ellsberg in 1908. Gerster used a gold plate in 1895, and Estor in 1916 reported 100 cases in which gold had been used. Cornioley used a platinum plate in 1929, Lluesma-Uranga used silver wire mesh, and Boldrey used a stainless steel wire mesh to cover cranial defects.

O. HUGH FULCHER ARTHUR A. MORRIS

Renewed interest in the use of metal for repairing cranial defects was effected by the use of Vitallium in 4 cases reported in 1941 by Geib. The use of this material was somewhat impractical since it was not flexible and had to be cast. Fulcher used tantalum on November 24, 1941, to repair a cranial defect at the suggestion of Captain F. R. Hook of the Naval Medical Corps. The tantalum plate used was 0.025 inch thick. Three perforations were drilled into the plate which had been previously made into the correct contour by means of a ball-peen hammer and a wooden anvil. The plate was then sterilized by boiling and it was used as an inlay to repair the cranial defect. The plate had to fit snugly and was placed in position without forcing. Pudenz demonstrated experimentally that tantalum was well tolerated by the tissues. Gardner in 1944 reported the immediate repair of cranial defects with tantalum in 2 patients who had compound comminuted fractures. Conley used tantalum wire to secure the plates in a patient from whom he had excised a large osteoma. Hemberger, Whitcomb, and Woodhall used triangular trimmings to secure the plate. Echols and Colclough applied the plate as an onlay beneath the periosteum. Mayfield and Levitch used tantalum wire to secure the plate in 20 cases. Harris and Woodhall demonstrated that tantalum was so well tolerated by the tissues that a pedicle graft could be used over the plate.

Gardner quoted Craig as observing that the brain pulsates in a trephined skull but does not in a closed one. This was indeed a most important observation. It represents the basis for advocating the repair of a cranial defect in as brief a time as possible. Furthermore, according to this observation the brain is in a pathologic motility when a

cranial defect exists. The pathologic motility of any tissue results in erosion and degeneration. When an aneurysm pulsates against the vertebrae the bone is absorbed. It is not difficult to understand that when the delicate brain tissue pulsates against the undersurface of the skull or even when adjacent blood vessels pulsate there would occur degeneration and subsequent gliosis. This represents the first explanation as to why epileptiform convulsions and other so-called post-traumatic sequelae will frequently develop many years after the original injury. In these instances there must be some pathologic process which is progressive and which is gradually bringing about those changes in the brain tissue necessary for the production of the convulsion.

Mayfield and Levitch demonstrated the importance of perforating the tantalum plate by using a solid plate that had to be sacrificed when an infection developed but were able to save a perforated plate under similar circumstances by aspirating the wound and administering penicillin locally.

Woolfe and Walker attempted to evaluate the different methods of cranioplasty in their classical article in which they presented their experience with methol-metacrylate. They thought that this resin was inert and had the advantage of being penetrated by x-ray. Voris thought that a contaminated or infected wound constituted a contraindication to cranioplasty.

The hazard of using tantalum near the frontal sinuses without ablation has been pointed out by Work, White, and others. White reviewed 151 late complications following repair of cranial defects with tantalum, Vitallium, and acrylate resin. He thought that autogenous bone graft was preferable when used near the frontal sinuses. He advocated the removal of any plate in a grossly infected wound. He thought that the defect should not be repaired for 2 months or longer after the injury and if infection had existed even more time should elapse. He concluded that a large defect could be repaired by the use of alloplastic materials with about the same safety as by using autogenous graft. He preferred to use autogenous graft for the repair of an orbital ridge.

TECHNIC OF TANTALUM CRANIOPLASTY

The tantalum plate should always be 0.015 inch thick or thicker. In many instances it should be 0.025 inch thick to afford adequate protection to the underlying brain. Perforations were always placed in the plate at intervals of about 1 cm. On the evening preceding the operation and after the scalp had been shaved, a piece of cardboard was placed over the defect and trimmed to the exact size. The cardboard was then placed on the metal plate which had been perforated and it was cut slightly larger. A portion of the skull homologous to that of the defect was selected and the size of the defect was represented by a blue pencil mark. The homologous area served as a mold and the tantalum plate was shaped to the correct contour with a ball-peen hammer and a wooden anvil. At intervals of about 1.5 cm. along the border of the plate small triangular trimmings were excised which permitted the border to be more inverted. The plate was sterilized by an accepted method (Figure 1).

If the cranial defect involved a frontal bone to the extent that no homologous area existed, the depression was filled with dental plaster until the desired cosmetic contour was achieved; the contour of the plate was then made to fit over the dental plaster. The operation was performed under local anesthesia which was supplemented by the intravenous administration of sodium pentothal when the patient desired to be asleep. The scars were excised and the cranial defect exposed. If there existed an underlying foreign body the dura was excised and the fibrous tract representing its path of travel was followed by coring it from the brain tissue. No attempt was ever made to remove the metallic foreign bodies unless they were readily accessible. The policy that one is not justified to incise healthy brain tissue to remove a deep seated metallic foreign body was rigidly practiced.

All dural defects were carefully repaired. This was always done by the use of fascia lata. In no instance was the plate ever laid directly over the cerebral tissues. The osseous border of the defect was then exposed and the periosteum was separated from the endosteum at the inner table. The periosteum was then reflected upward and backward exposing the desired area of the outer table. The prepared tantalum plate was then placed over the defect to determine the desired size. If necessary, it was trimmed with tin shears or heavy scissors.

With the tantalum plate covering the defect the borders were delineated by means of a sharp periosteal elevator. By means of a T-shaped chisel with a vertical blade about 0.02 inch in length a groove was cut along this mark and the outer diploe was removed to this depth with a chisel to prepare the ledge (Figure 2a). The plate was then placed in situ, the border was re-

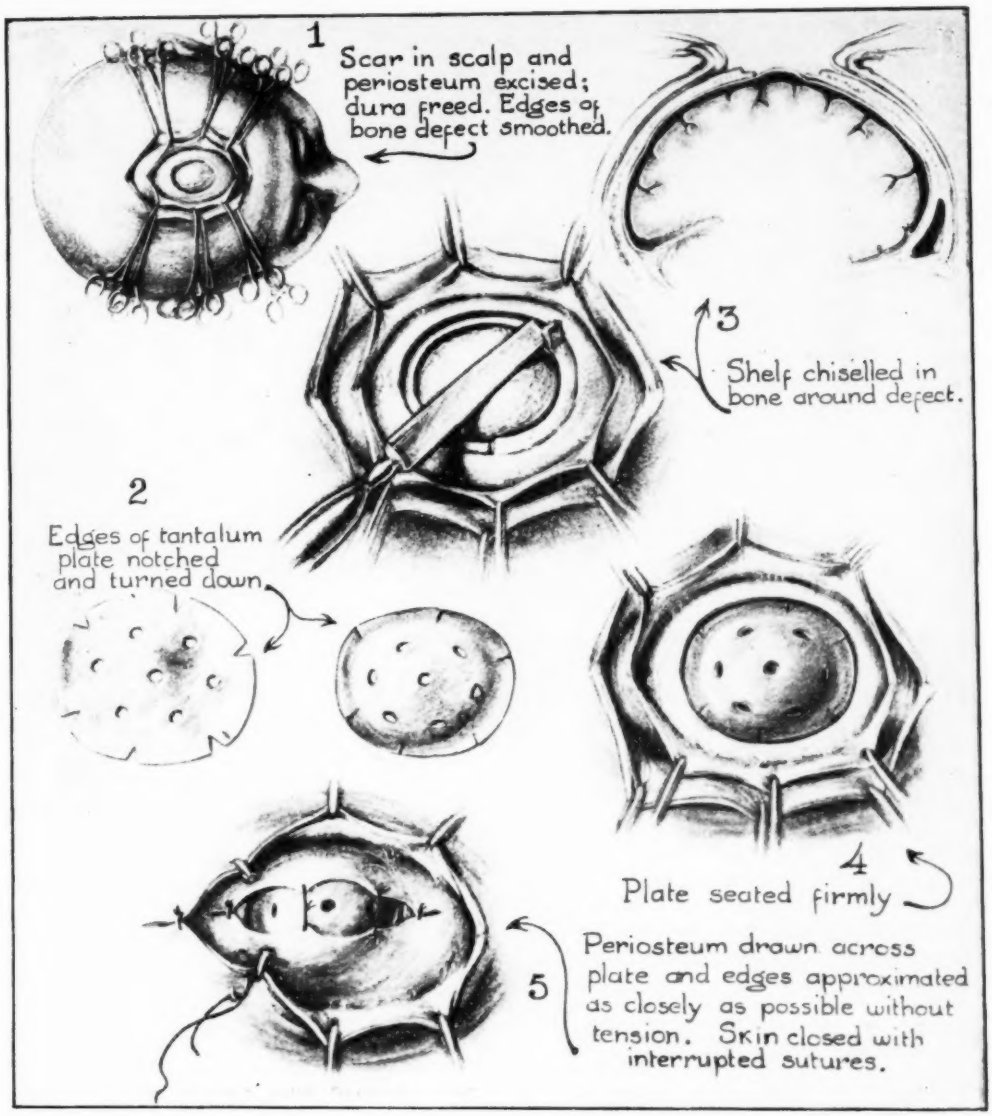

1
Scar in scalp and periosteum excised; dura freed. Edges of bone defect smoothed.
3
Shelf chiselled in bone around defect.
2
Edges of tantalum plate notched and turned down.
4
Plate seated firmly
5
Periosteum drawn across plate and edges approximated as closely as possible without tension. Skin closed with interrupted sutures.

FIGURE 1. The preparation of the tantalum plate and a technic of cranioplasty. (Reprinted courtesy of the Medical Annals of the District of Columbia.)

adjusted, if necessary, and pressure was made on the dome with a wooden hammer while the latter was gently tapped with a mallet which made the border of the plate spread out to secure it firmly (Figure 2b). The edges of periosteum were pulled toward each other with absorbable sutures and the scalp was closed with two layers of interrupted silk sutures. Penicillin was usually injected into the wound.

It was usually necessary to aspirate the wound once or twice during the convalescence because of the accumulation of serosanguinous fluid. After each aspiration penicillin was injected locally.

At times it was desirable to vary this technic. Instead of making a prepared ledge around the defect as described, the outer table of the rim was split about 0.5 cm. with an osteotome and elevated. The plate was then slipped into this bed and the outer table closed over its border. It was soon snugly secured by osseous formation.

When the defect was very small, the tantalum plate could be prepared according to the method of Mount. It was never deemed wise to use screws, triangular trimmings, or wire to anchor the plate. Every effort was made to avoid forcing the plate into the prepared ledge as the constant pressure produced by the deflected border would cause erosion of the bone and subsequent necrosis of the overlying soft tissue.

When the wound of the scalp could not be closed, a sliding graft was effected by making appropriate incisions. The resulting exposed areas were over the pericranium and were covered by split skin grafts. The tantalum plate was always covered by normal scalp that was not under tension.

A series of 16 cranioplasties were reported in 1948. All of these patients had received their wounds during combat duty; they were either sailors or marines. There were no deaths; the ages varied from 19 to 26 years. All of the operative wounds healed promptly except that of 1 patient; in this instance the plate had to be removed but was later replaced successfully. The average length of time between the injury and cranioplasty was 3 months, 19 days.

Among this group 2 patients had had 3 previous operations, 3 patients had had 2 previous operations, and 7 patients had experienced only 1 previous operation. Two patients had metallic foreign bodies present within the calvarium which were not removed. Four patients had osseous fragments within the skull or within the brain proper which were removed. The cultures made from them revealed no bacterial growth.

All the patients presented symptoms at the time of admission. None was able to run, lift, or endure vigorous exercise because of a bulging of the scalp overlying the defect associated with the sensation of vertigo or threatening syncope. All were fearful of getting struck over the unprotected area. All of the patients were conscious of their disfigurement and desired to avoid social gatherings. They were annoyed by the frequent questions asked of them and desired plastic operations before proceeding to their homes. Seven of these had tenderness over the defect, of whom 5 suffered with headaches; 1 had visual disturbance, and 1 had no additional symptoms. One patient had headaches and visual disturbances. One had partial paralysis of a left upper extremity associated with an electric shock referred to this appendage upon flexing the neck. One had paresthesia of both lower extremities. Another had headache and nausea. One had a left hemiplegia and anosmia. None of these patients presented the symptom of convulsive seizures. One patient had a convulsion caused by striking the cranial defect against the corner of the bedside table. There existed no correlation between the symptoms and the size of the defect.

Following successful cranioplasty these patients could run and engage in physical exercise. They were cured of the pulsations of the scalp. The normal contour of the skull had been restored and there existed no tenderness. They had lost their anxiety regarding social functions and used the expression universally that "their heads felt secure again." Two of this group continued to have headaches which were milder. The visual disturbances of the 2 patients were not affected by the cranioplasty. The paresthesias of the 2 patients had entirely disappeared. All had experienced improvement and all were grateful for the surgical therapy.

ANOTHER series of 10 cranioplasties has been included in this report because of complications. The ages of this group varied from 12 to 42 years. There were 8 males and 2 females. One woman and 3 men had recurrent convulsions; 2 of these had large cranial defects in the right frontal region, 1 had a congenital defect of the dome of the cranium, and the female patient had an unrecognized healed depressed fracture in the left frontal region. She had developed convulsions six months after the original injury. The patient with the congenital defect had suffered with convulsions all his life, and the other 2 patients had developed convulsions 7 and 18 years respectively after the original injuries. The old depressed fracture of the patient was removed and a tantalum plate was inserted but the convulsions continued. About nine months later, an osteoplastic flap was made and a large cyst was excised from the left frontal lobe. She has had convulsive seizures only fol-

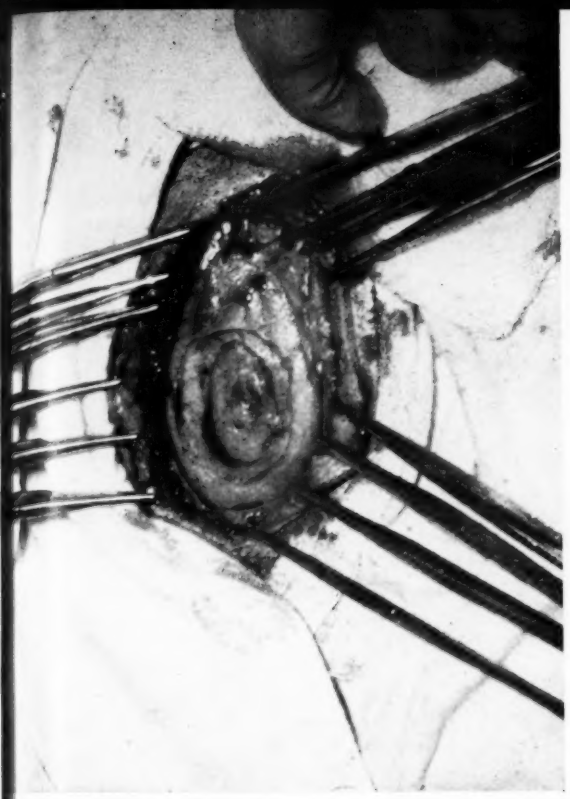


FIGURE 2*a (above)*. Preparation of bony ledge about defect. *b (below)*. Tantalum place in situ on bony ledge.

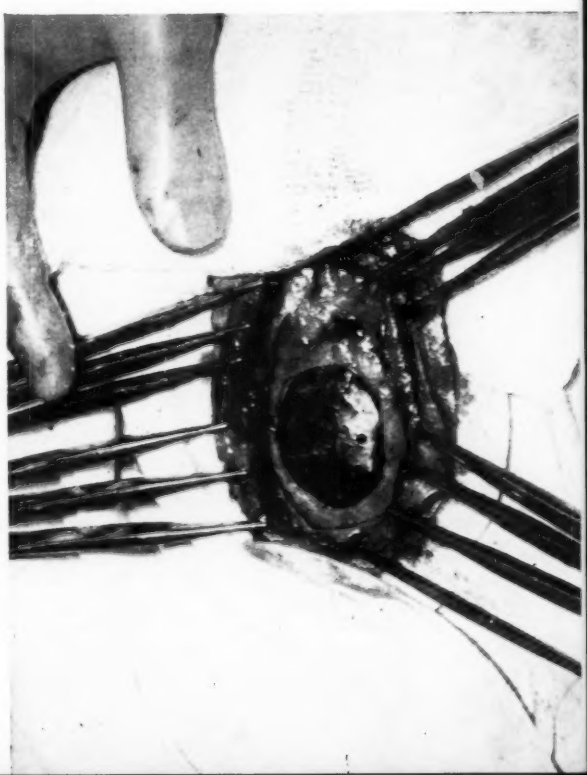
lowing overindulgence in alcoholic beverages.

A man, 25 years of age, continued to have convulsions after the repair of his right frontal defect. The right frontal sinus was ablated and the nasofrontal canal was plugged with bone before the plate was inserted. The convalescence was uneventful. The congenital defect had been repaired with a resin plate in 1943 by another surgeon. When the plate was removed the underlying arachnoid appeared grayish-white and thickened, and this was interpreted as evidence of chronic irritation. The defect was repaired again by a tantalum plate 0.015 inch thick by the usual method. Great attention was paid to the superior longitudinal sinus to make certain that it was not occluded by pressure. He was not relieved of the convulsive seizures.

A male patient, 30 years old, had received the original injury 20 years previously. One attempt had been made by another surgeon to repair the defect with celluloid but the plate had to be removed because of infection. When the tantalum plate was applied with a border adjacent to the right frontal sinus it was thought that the condition did not require ablation of the sinus. The usual method was employed and the convalescence was uneventful for about three weeks. The patient had returned to work when he developed acute sinusitis. A few days later he became suddenly unconscious associated with a convulsive seizure; he was returned to the hospital in a comatose condition. The autopsy revealed a ruptured abscess of the right frontal lobe of the brain which had been caused by the metal plate eroding the frontal sinus. This case emphasizes the hazard of employing a metal plate in the vicinity of a nasal sinus.

Two male patients, 34 and 30 years of age, had cranial defects in the right fronto-parietal and the right parieto-occipital regions respectively. Each cranial defect was approximately 5 by 3 cm. in size. The dominant symptom in each case was dizziness. Their original injuries had occurred 12 and 5 years previously, respectively. All symptoms were completely relieved by cranioplasty.

A female patient, 24 years of age, received the original injury six years previously. There was a cranial defect 6 by 3 cm. in size in the left occipito-parietal region. The chief complaint consisted of pulsations and tenderness over the defect associated with recurrent attacks of severe headaches. Exploration revealed that underlying this defect there was much brain destruction



replaced by fibrous tissue which enclosed a sterile abscess. The fibrous tissue together with the abscess were excised, the dura repaired, and a tantalum cranioplasty performed. The convalescence was uneventful. The cranial contour has been restored and she has been free of all symptoms.

A boy, 15 years of age, had almost been electrocuted while crawling over a freight car when his head made contact with an electric cable of high voltage. About three months later a large portion of the dome of the cranium became a sequestrum and was removed. The dura was intact and the superior longitudinal sinus was patent. Subsequently, a tantalum plate was applied which was covered with scalp by utilizing the sliding graft technic. Within an hour after the operation the patient developed convulsions associated with unconsciousness which continued with accumulating gravity until the plate was removed about five hours later. It was ascertained that the plate had become flattened during its application and had occluded the superior longitudinal sinus. The convulsions ceased within a few hours and the patient became conscious.

About nine months later the plate was reapplied with due allowance of space for the longitudinal sinus (Figure 3). The convalescence was uneventful. He has been completely free of all symptoms and has advanced with his class in school.

A boy 12 years of age had been injured in an airplane accident during October, 1948, at which time he suffered a depressed fracture which left a defect about 3 by 4 cm. in the left frontal region. A cranioplasty with tantalum was done on March 29, 1949, while the wound was still granulating. Convalescence was uneventful due largely to extensive use of chemotherapy. The presenting symptom was tenderness over the cranial defect associated with dizziness upon change of position. All symptoms disappeared following treatment.

A Negro male, 42 years of age, received a comminuted depressed fracture in the right parietal region when he was struck by a hammer. Under anesthesia the wound of the scalp was excised, and the fragments of the depressed fracture were removed revealing the dura to be intact. A tantalum plate was applied immediately. During convalescence the fluid was repeatedly aspirated and penicillin was injected locally. The patient had an uneventful convalescence. He did not experience the psychologic and physiologic results of a cranial defect.

COMMENTS

The patients in this series were not relieved of convulsions by cranioplasty. Since the seizures of 2 patients developed so many years after the original injury one must surmise that the existence of the cranial defect permitted the development of pathologic physiologic processes which eventually created the required conditions. If the cranioplasty had been performed before the onset of the recurrent convulsive seizures, it might have been possible to stop the pathologic trend and the sociologic and economic status might have been preserved in each case. Upon this basis an early cranioplasty is recommended. Therefore, the probability of avoiding epilepsy appears to warrant the additional risk of infection by performing the tantalum cranioplasty at the time of treating the original injury, if at all feasible. Modern methods of chemotherapy have reduced the risk of infection materially.

The only tragedy occurred as a result of the tantalum plate eroding the frontal sinus. This experience suffices to condemn the employment of any alloplastic material about the nasal sinuses. Either the nasal sinus should be ablated and the naso-frontal canal plugged with bone or autogenous grafts should be employed. We have now adopted the policy of using the tantalum plate in the frontal region to obtain the desired cranial contour. The plate is not permitted to extend to the nasal sinus. The defect between the nasal sinus and the plate is repaired by autogenous cancellous bone. The presence of tantalum appears not to inhibit osteogenesis.

A tantalum plate can be placed over a venous sinus with due precaution. In one instance the plate did occlude the longitudinal sinus by pressure which produced unconsciousness and convulsions. A tragedy was prevented only by its removal. At least 0.5 cm. of space must exist between a sinus and the overlying plate. Also it is necessary to do frequent aspirations of accumulated fluid, otherwise the pressure exerted will occlude the venous channel with the same result as observed in the patient previously described.

Tantalum cranioplasty performed before the scalp wound had entirely healed was done successfully in 1 patient. This policy, however,

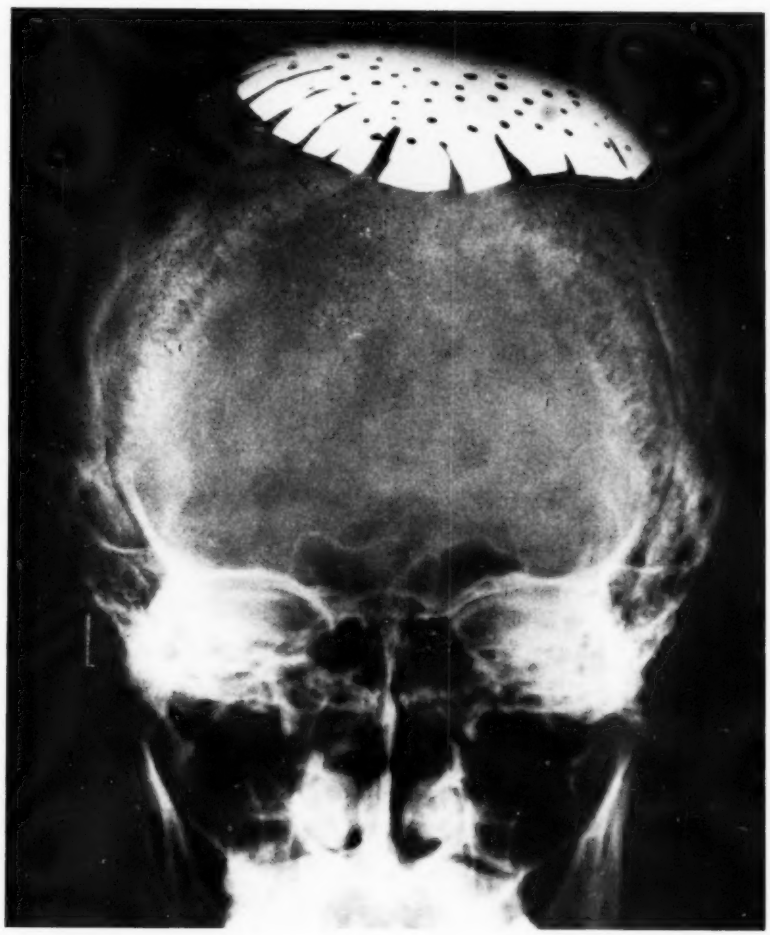


FIGURE 3. Perforated tantalum plate used successfully over superior longitudinal sinus.

should be condemned as it does not represent the best surgical principles. The chance of failure is greater and the risk to the patient is needlessly increased. There did exist in this particular instance a combination of circumstances which required that the cranioplasty be done at that time or not at all as the patient lived in Alaska.

All symptoms except convulsions were relieved by cranioplasty. Vertigo, local tender-

ness, pulsations, the sensation of syncope, and hyperirritability to noises disappeared in all patients. The cosmetic results were satisfactory in all individuals. The ability to engage in physical exertion was uniformly restored.

The use of tantalum for cranioplasty has great advantages but it has not entirely replaced autogenous grafts. The two may be wisely used together; this element does not inhibit osteogenesis. Under certain conditions the tantalum plate should be supplemented by autogenous grafts. Good surgical principles must be employed. The physiologic reactions of tissues to pressure should be kept constantly under consideration.

One of the authors recently visited several veterans hospitals to interview patients who had experienced failures with tantalum cranioplasty. The chief reason for failure had been the improper insertion of the plate. In some patients the plate had evidently been forced into the required contour and the rebound pressure had produced erosion of the bone and scalp. Several patients were examined who demonstrated that the triangular trimmings or screws used to anchor the plate had eroded the scalp. In one instance a much larger plate than was required had been used as an onlay over the pericranium. The border had eroded the scalp at various places. A few plates had been used which were too thin and had been bent, hence they were causing pressure symptoms. One large plate without perforations had been used and the overlying scalp incision had separated. The perforations not only tend to prevent the accumulation of fluids beneath the plate but also allow increased development of vascularization about the scalp incision. Blood vessels pass through the perforations.

It is still true that no method of surgical therapy is any better than the one who employs it. Numerous junior surgeons in the military services were able to use tantalum for cranioplasty. These doctors did restore many disabled officers and men to active duty. They were able to shorten the convalescence for many others.

CONCLUSIONS

1. All cranial defects should be repaired. There was evidence that a cranial defect could permit the occurrence of pathologic processes that caused epilepsy. Cranioplasty did not cure epilepsy but might have prevented it.
2. The "defect syndrome" disappeared following successful cranioplasty.
3. Cranioplasty provided satisfactory cosmetic results.
4. Tantalum is a superior material to use for cranioplasty but it does not entirely replace autogenous grafts.
5. No alloplastic material should be used near a frontal sinus unless the latter is ablated.
6. A metal plate placed over a venous sinus is somewhat hazardous but it can be done if proper precautions are taken to prevent occlusion by pressure or accumulation of fluid.
7. Good surgical principles are not pursued when one performs a cranioplasty in the presence of a granulating wound.
8. The chief cause of poor results with tantalum cranioplasty was the failure to be guided by good surgical principles and the disregarding of tissue reaction to constant pressure.

Bibliography furnished on request

COMING MEETINGS AND POSTGRADUATE COURSES

American Psychiatric Association, Washington, D. C.
Second Mental Hospital Institute, at St. Louis University Auditorium, St. Louis, Missouri, October 16-19. Equivalent to a postgraduate seminar, the 4-day workshop will cover administration and business management, community and public relations, clinical practices and problems, and inservice education and training. Attendance fee is $50. Advance registration should be made with Director, A.P.A. Mental Hospital Service, 1624 Eye St. N.W., Washington 6, D. C.

The Ambulatory Fracture Association, Chicago, Illinois
Eleventh annual meeting, at the Gibson Hotel, Cincinnati, Ohio, October 16-19

University of Minnesota, Minneapolis
Continuation course in female and male infertility, at the Center for Continuation Study, September 28-30, intended for physicians specializing in obstetrics and gynecology. Key topics include psychosomatic aspects of sterility, the investigation and management of the infertile couple, the management of amenorrhea, and artificial insemination.

Continuation course in neurologic roentgenology, at the Center for Continuation Study, October 30-November 4. Visiting faculty members include: Arthur E. Childe, Winnipeg; Philip J. Hodes, Philadelphia; Dabney Kerr, Iowa City, and Knut Lindblom, Stockholm, Sweden.

Splenectomy in Leukemia

OSCAR B. HUNTER[1] AND PAUL C. KIERNAN[2]

GEORGETOWN UNIVERSITY MEDICAL CENTER, WASHINGTON, D.C.

In no other field have the advances in medical achievement made during the last war been felt as in the field of hematology. The availability of blood in adequate quantities, with a minimum of reactions, the availability of antibiotics to sustain a patient during a period of lowered resistance due to deficiency of leukocytes, and the availability of coagulating agents to stop hemorrhages, are only a few of the achievements which have rendered all previous experience in the hematologic therapy of leukemia obsolete.

The complication of splenomegaly has been an unsolved problem in leukemia but only recently has the idea of hypersplenism[1-3] been conceived and adequately described. Two years ago one of us (O. B. H.) described the problem of hypersplenism as associated with leukemia and other malignant diseases.[4] This recognition has led us to search for the complication in all of our cases of leukemia.

The concept of hypersplenism is seen in three specific types, with one or all of the types being present contemporaneously. Hemolytic anemia may be initiated due to sequestration and destruction of the red cells within the dilated sinusoids of the enlarged splenic pulp. Splenic neutropenia due to destruction of the white cells by the spleen and thrombocytopenic purpura due to phagocytosis by the spleen, can and do exist either in isolated instances or as a part of a panhematocytopenic picture in leukemias.

This pertinent problem has led us to investigate the possibilities of ridding the patient of his symptoms by surgical removal of the spleen. Other situations associated with a large spleen, such as infarction, with or without fever of an undulating type, have further led us to consideration of the use of splenectomy to eliminate these annoying symptoms.

At the present time the availability of blood to compensate for blood loss and deficient production together with antibiotics to make up for any deficiency in leukocyte resistance, and the use of coagulants to overcome local hemorrhages, have removed from splenic surgery the great deterrents which previously rendered it so dangerous.

It is interesting to look back and see that other workers, in a more difficult time, considered the use of splenectomy for relief of symptoms in leukemia and found it to be a successful and helpful modality. Dr. W. J. Mayo, in 1926[5] reported on 500 cases of splenectomy of which 53 were performed in cases of leukemia. In 1928[6] he further elucidated on these cases and remarked:

> "Splenectomy is suggested in these cases by the fact that any treatment which reduces the size of the spleen improves the condition of the blood and thereby the condition of the patient. Patients in this group have lived and have been able to work for a number of years after splenectomy." Further he remarked: "The results are better than they appear because in cases of possible splenomyelogenous leukemia when the condition of the blood approaches normal after splenectomy, it is assumed the disease was not proven splenomyelogenous leukemia and the case is classified with the splenic anemias or left unclassified. These cases will be explained later in the light of future knowledge."

This far-seeing wisdom is now being accepted as worth while in leukemia. Dr. Mayo was not alone in his experience with splenectomy in such cases. Isolated instances of splenectomy in leukemia have been reported with varying periods of survival. Wieder[7] in 1931 reported the case of a 4½-year-old boy who lived for 2 months postoperatively with improvement. Gordon[8] has reported the case of a 5-year survival; Carding, Carlill, and Pulvertaft[9] reported a case surviving one year. Lower and Bull[10] reported a one-year survival. Haggard[11] in the discussion of Lower and Bull's cases reported a 5-year survival. Beer and Rosenthal[12] reported poor results in 3 cases. Wheatley[13] reported a case of 11 years' survival.

[1]Instructor in Clinical Medicine, Georgetown University Medical Center, Washington, D.C.

[2]Associate Professor of Surgery, Georgetown University Medical Center, Washington, D.C.

PAUL C. KIERNAN

OSCAR B. HUNTER, JR.

THESE reports are of particular interest in the light of the literature of the decade between 1930 and 1940. During this time one of the primary contraindications to splenectomy was described by most authors as leukemia, either granulocytic or lymphocytic. That concept has persisted to the present time and it is the opinion of many men practicing today. The opinion is present in most textbooks. In most papers on splenic surgery the contraindication is mentioned in a prominent position.

From our experience during the past two years the following cases are presented:

CASE REPORTS

Case 1—This 38-year-old white female was first diagnosed as having chronic lymphocytic leukemia in April, 1943. At no time was the disease very severe. She was treated by means of transfusions, together with some x-ray therapy. Early in 1948 the patient developed an enlargement of the spleen with hemolytic anemia. The spleen had descended to a distance of 10 cm. below the right costal border. During the first part of 1948 she required approximately 2 transfusions a month. In April the need for transfusions was increased to 2 every 10 days to 2 weeks. In June it was decided that splenectomy was indicated for the hypersplenism, and on July 15, 1948, a 1,500 gm. spleen was removed. The patient was transfused and the blood count remained at a 4 million level, as indicated by Figure 1; this transfused level was maintained by transfusions every 2 months without difficulty.

The patient returned to work as a stenographer and worked continually until March, 1950, when she suffered from an attack of influenza during a generalized epidemic. Following the influenzal infection the patient developed an upper respiratory bacterial infection, and on March 31 she first noticed an eruption which had the aspects of a herpes zoster. It progressed to cover the entire body. All available antibiotics were utilized without avail and the patient died from this infection on April 6, 1950.

Case 2—This female patient was initially seen in June, 1949, at which time an abnormal blood picture, suggestive of chronic lymphocytic leukemia, was seen. The leukocyte count was 5,200, with 50 per cent abnormal lymphocytes. The patient continued to run this abnormal leukocyte count with a feeling of being "worn out" until December, at which time the red cell count was reduced to 2,940,000, the leukocyte count 4,900, with 59 per cent lymphocytes and 240,000 platelets. This picture continued with frequent blood transfusions being required until January, 1950, when bone marrow examination revealed a hypoplastic marrow, and the peripheral blood picture was clearly indicative of chronic lymphocytic leukemia. The red cell count reduced at an abnormal rate, and transfused red cells would maintain the count for no more than 10 days.

During the month of February the patient received 8 transfusions of 500 cc. of blood, and the red cell count continued to fall. Stool urobilinogen was elevated to 277 mg. per cent, and on February 27 the red blood cells numbered 2,240,000; white blood cells 400, with 54 per cent lymphocytes and 3 per cent blast forms; platelets 55,000. This was interpreted as splenic panhematocytopenia and the patient was hospitalized for splenectomy.

After adequate transfusions splenectomy was done on March 2, 1950. The removed spleen weighed 819 gm. Microscopically, the spleen showed a typical enlargement with hyperplasia of the lymphoid elements; the lymph nodes at the hilum showed the architecture of a giant follicular lymphoblastoma.

Postoperatively the patient progressed satisfactorily and as can be seen by Figure 2 the blood picture improved generally. This was enhanced by the administration of liver intramuscularly. She was discharged from the hospital on March 13, 1950, and was ambulatory at that time. On March 21 she was seen in the office; her blood count at that time showed red blood cells 2,960,000; white blood cells 1,400, platelets 118,000. The differential count was relatively normal.

It was expected that the patient would have to be maintained on blood transfusions similar to case 1. However, on March 22 she was confined to her bed at home with a fever and was found to have a rapid pulse and a slight cough. She was admitted to the hospital but in spite of all supportive measures her course was that of a fulminant influenza with cardiac failure, and she died on the following day after an illness of less than 36 hours.

Case 3—This 52-year-old white female was first seen on January 2, 1945. She had a red blood cell count of 4,190,000, white blood cells 25,000, and a definite increase in myelocytes. She was diagnosed at that time as having chronic granulocytic leukemia. Her course was very benign and she was given x-ray therapy over the spleen. She continued to get along excellently until early in 1949, when she developed an afternoon elevation of temperature and some increase in the leukocyte count. She was treated at that time with antibiotics on the presumption that she had some bloodstream infection, but there was no improvement.

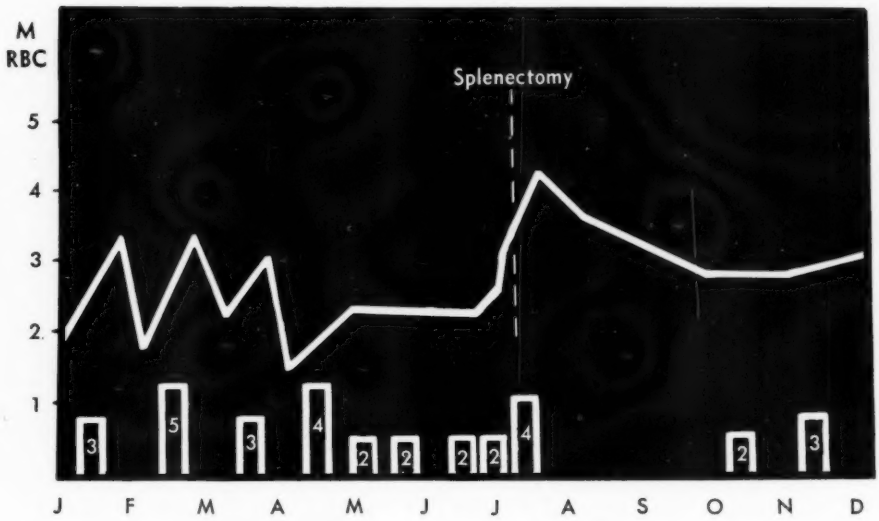


FIGURE 1 *(Case 1)*. Chronic lymphocytic leukemia, 38-year-old white female, with primarily hemolytic anemia.

Nitrogen mustard was tried with some improvement for a short time, but the patient did not respond well following this.

During the last half of 1949 transfusions were required and an elevation in the reticulocyte count was noted. The leukocyte count steadily rose to 85,000. The patient was confined to bed in December and intravenous urethane was utilized in an attempt to restrain the leukocyte count, but this gave no improvement. The red cell count began to fall late in December, and shortly before the period of hospitalization noted on Figure 3 her count was: red blood cells 2,740,000, white blood cells 88,000, and platelets 96,000. The fragility test showed some increase in osmotic fragility. Severe pain was noted in the left upper quadrant prior to hospitalization.

Splenectomy was performed on February 3, 1950, and a 1,750 gm. spleen was removed. The patient gradually improved during the following month but there was considerable difficulty from the point of view of thrombophlebitis. She suffered from migratory thrombophlebitis which has persisted up to the present time. At this time, however, it is less than previously noted. This patient has been maintained on 1 to 2 transfusions a month since splenectomy.

Case 4—This 47-year-old white male was first seen in September, 1949, at which time he was found to have a chronic myelogenous leukemia. He had been treated with urethane orally but had become nauseated by the drug and intravenous urethane was utilized. Because of his poor response to the urethane therapy he was admitted to the hospital in February, 1950, for further study. At that time it was discovered that he suffered from hypersplenism. The blood count was: red blood cells 2,660,000, white blood cells 192,000, platelets 837,000. The reticulocyte count was elevated; urobilinogen was 168. Observation of the bone marrow revealed a hyperplasia of all elements, particularly in the red cell series.

Because of the hypersplenism the patient was operated on following preparation with transfusions. A 2,500 gm. spleen was removed on February 24, 1950. This spleen revealed a considerable number of gross and microscopic infarcts, surrounded by phagocytes of all varieties, and there was some extramedullary hematopoiesis. This patient has made an outstandingly rapid recovery and was able to leave the hospital three weeks after admission. Since operation his course has been excellent, he is back at work, and his blood picture remains satisfactory without transfusions. His last blood count was taken on May 11, at which time the red blood cells numbered 3,710,000, white blood cells 120,000, and platelets 204,000.

Case 5—This male patient was admitted on April 14, 1950, as a "terminal myelogenous leukemia" patient with a red blood cell count of 2,440,000, white blood cells 160,000. Examination revealed a huge spleen occupying the entire abdomen. Further studies of the blood and bone marrow showed an elevated reticulocyte count, hyperplasia of all marrow elements, with fall in platelets in the peripheral blood. It was decided to splenectomize the patient after adequate preparation with blood. On April 14 a 7,000 gm. spleen was removed which showed marked enlargement of the red pulp with extensive phagocytosis. In addition there were many areas of gross and microscopic infarction and destruction of the splenic tissue. These areas were surrounded by large giant cells and within the viable areas there were some evidences of extramedullary hematopoiesis. The patient made an immediate satisfactory recovery and was discharged from the hospital on May 11.

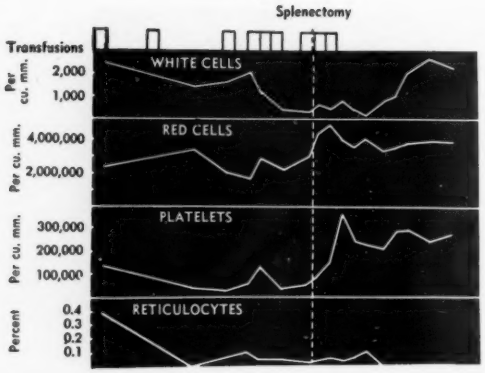


FIGURE 2 *(Case 2)*. Chronic lymphocytic leukemia, 47-year-old white female with panhematocytopenia.

The patient was readmitted for a phlebothrombosis after the platelet count had risen to over a million. At the present time he is on dicumarol and will be continued on this therapy for a period of 6 months. His leukemia appears, nevertheless, to be satisfactorily controlled.

DISCUSSION

SELECTION of cases for surgery is based on definite indications. These consist of proving the presence of hypersplenism in such a severe degree that it endangers life. This may be any one of the three forms of hypersplenism or of combinations of the three. The hemolytic anemia is usually the most serious condition because it presents itself earliest. The others follow and in the cases described many developed panhematocytopenia before splenectomy brought relief.

The following laboratory aids have been helpful in selecting cases for surgery:

Hemogram—The red cell count showed a constant fall which was not reversible by transfusion of compatible cells except in excessive amounts.

Reticulocyte count—In almost all instances an elevation of the reticulocyte count was a noteworthy feature.

Stool urobilinogen—All patients showed an elevated stool urobilinogen while hemolytic anemia was present.

Coombs test—This test was noteworthily poor as a diagnostic aid in our series—only 1 patient was positive.

Leukocyte count—In a number of instances the leukocyte count showed a lowering of the circulating leukocytes; the granulocytic leukemias usually had a rise in young elements.

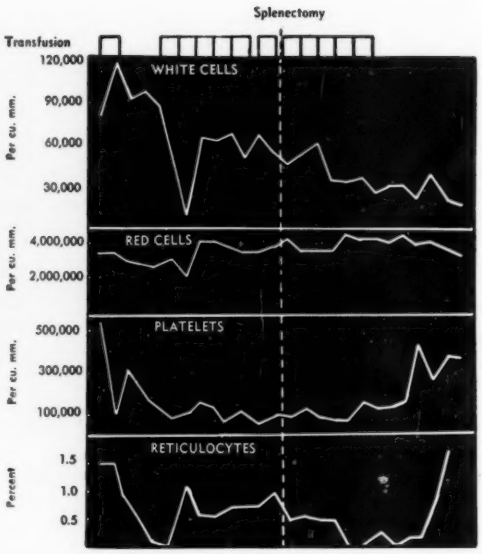


FIGURE 3 *(Case 3)*. Granulocytic leukemia with hemolytic anemia and thrombocytopenia, 52-year-old white female. Leukemia showed acute exacerbation associated with splenic infarction.

Leukocyte count—In a number of instances the leukocyte count showed a lowering of the circulating leukocytes; the granulocytic leukemias usually had a rise in young elements.

Platelets—A number of cases showed a lowering of circulating platelets.

Bone marrow—In almost all cases a hyperplasia of the marrow elements, particularly of those that were lowered in the peripheral blood, was seen. The exception to this was the lymphocytic leukemias. A depression of the normal elements was noted and in case 1 a marked increase in the lymphocytes was present in the marrow.

Transfusion test—In all cases where hemolytic anemia was present a transfusion test was made to determine the life span of circulating red cells. In all instances the red cell count continued to fall despite replacement. This feature indicated clearly a hypersequestration of the circulating red cells and their destruction.

SURGERY

Splenectomy is performed without difficulty in these cases if particular attention is paid to

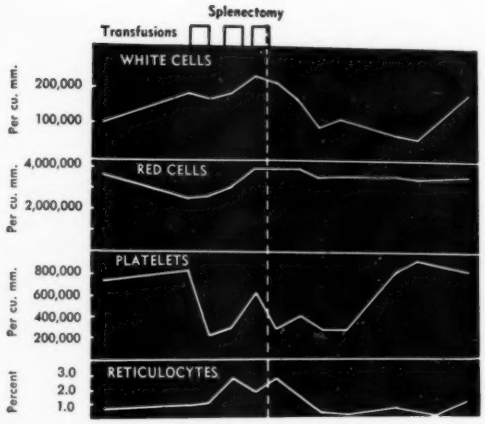


FIGURE 4 *(Case 4)*. Hemolytic anemia and thrombocytopenia, 47-year-old white male. Leukemia showed acute exacerbation associated with splenic infarction.

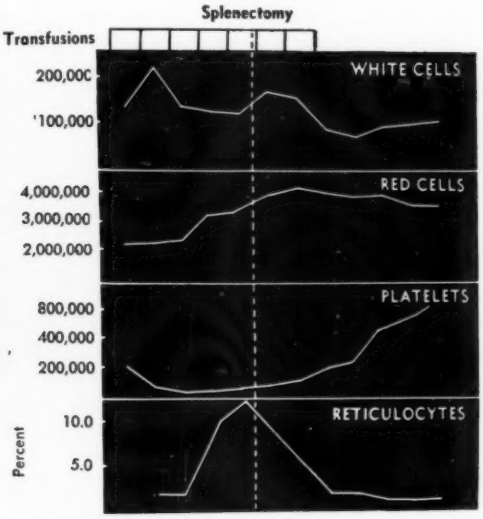


FIGURE 5 *(Case 5)*. Hemolytic anemia and thrombocytopenia. Leukemia showed acute exacerbation associated with the splenic infarction.

accurate and complete hemostasis. The approach may be abdominal, thoracic, or combined. We have preferred the transabdominal procedure which, if carried out through a left rectus muscle-splitting incision, affords adequate exposure and does not entail the risk of postoperative bleeding into the chest, as would be possible after the "combined" or thoracic incision.

Paradoxically, removal of a huge spleen is more frequently attended with less difficulty than the removal of a normal or slightly enlarged one. In leukemic cases, except when massive splenic infarction with resultant perisplenitis exists, the spleen is not often surrounded with vascular peritoneal adhesions such as are present in individuals with splenomegaly in longstanding portal hypertension. An aid in the removal of a large spleen is elevation of the organ from its peritoneal bed, quick packing of such to control bleeding, and then careful ligation of the splenic pedicle. Bleeding from the adhesions is controlled after the organ has been removed. When there is difficulty in delivering excessively large spleens, as in case 5 (7,000 gm.) the introduction of air via a catheter into the subdiaphragmatic space abolishes the existing negative pressure which acts to hold the organ in situ. Care, of course, must be taken to search for and remove any accessory spleens which usually are found in the region of the hilum.

Anesthesia, as in all surgery, plays a most important role. Adequate relaxation is required and yet the blood pressure must be maintained at a sufficiently high level to assure adequate control of bleeding immediately following removal of the spleen. This precludes the possibility of hemorrhage postoperatively. In panhematopenia or hypersplenism affecting the platelet count with one or the other formed elements of the blood, care must be taken to insure meticulous control of bleeding for, in contrast to individuals with primary thrombocytopenia, in this disease, the postsplenectomy platelet rise, particularly in older individuals, is slow. There is, we think, a definite retardation of wound healing in these patients, therefore protection against wound disruption is in order.

RESULTS

THE satisfactory results have proved the diagnosis in each case. In the first case the patient made an immediate recovery and required transfusion of 1 to 2 pints of red cells only every 6 weeks. This patient lived on this regimen for almost 2 years when she died as the result of a fulminating generalized herpes zoster during an influenzal epidemic.

In case 2 the patient died from an influenzal myocarditis 48 hours after she had visited the office. Her death also occurred in the midst of an influenzal epidemic. This patient, as can be

noted from the history and from Figure 2, had a falling red cell, leukocyte, and platelet count. Following splenectomy, there was improvement in all elements, and the patient was in excellent health and was working until two days before her death.

The case 3 patient had a granulocytic type of leukemia. She developed an acute hemolytic anemia following a chronic form. The leukocyte count initially rose as did the fever. Subsequent to the splenectomy the leukocyte count returned to 25,000, the red cell count was maintained without transfusions, and the platelet count and reticulocyte count rose. This patient is still living.

Case 4 presented a situation of rapidly rising leukocyte count with fall in the red cell count and depression of platelets. The reticulocyte count rise was associated with the onset of severe hemolytic anemia and evidence of hypersplenism. Following splenectomy, the leukocyte count fell, with maintenance of the red cell count, once more elevation of the leukocytes, and the return to normal of the reticulocytes. This patient also had a marked infarction of the spleen which was causing severe fever and depletion of energy. Splenectomy produced a remarkable clinical result, and the patient has again returned to an active life.

The last case, described as a "terminal leukemia patient" showed marked elevation of the leukocyte count and depletion of the red cell count, with elevation of reticulocytes and some depression of the platelets. Splenectomy eliminated the marked hemolytic disease, and the leukocyte count was controlled to some extent. This spleen was also involved by large infarcted areas. This particular patient has been troubled by thrombotic phenomena during his entire postoperative course and at the present time is on anticoagulant therapy but appears to be making progress slowly. The leukocyte, red cell, and platelet values appear to be being maintained in a fairly normal fashion.

From these cases, the most remarkable features noted following splenectomy are elimination of the hemolytic anemia and lowering of the leukocyte count. The hypersplenism has received considerable comment, but of equal note is the lowering of the leukocyte count. These patients are frequently described as acute exacerbations of chronic leukemia. Results of splenectomy indicate that the acute exacerbation is primarily associated with the spleen, and it would appear highly likely that from the gross infarction of the spleen there has been absorbed a leukopoietic substance, stimulating the bone marrow to produce immature cells. Their elimination is a feature in the postoperative marrow. The fever, so prominent in the preoperative course, is absent in the postoperative course.

In case 3 the infarction was the most prominent symptom. Severe left upper quadrant pain was most marked with respiration. At operation, infarction with early organization and adhesions were noted between the capsule of the spleen and the parietal peritoneum. Postoperatively the patient was relieved of the symptoms. This adds further to the concept of antagonism and protagonism as the cause of leukemic blood pictures. In these cases evidence of a protagonistic element in the necrotic spleen is much in evidence.

There is a decided difference between the results in the lymphocytic and myelocytic leukemias. The patients with lymphocytic leukemia in this group are both dead; 1 patient, however, lived 2 years before her death; the second patient only 1 month. Nevertheless, the postoperative course did not show the return of a self-sustaining erythropoietic activity. The lymphocytic leukemia still persisted in its destructive influence and suppression of the red cell count. It is these patients that have been described as the most worth while by other authors, Welsh and Dameshek[14] and Rosenthal.[15]

The granulocytic cases, on the other hand, have done well. The one outstanding feature complicating their course has been the excessive tendency to thrombosis. These patients have suffered severely from generalized thrombotic phenomena which in 1 case, for instance, have caused prolonged fever elevation and scattered pains throughout the body. Treatment with anticoagulants has eliminated this finding and offers much to overcome this particular symptom in these cases. The reason for the increased thrombotic tendency is certainly not the result of excessive numbers of platelets alone although occasionally the platelet count does rise to over a million. Of note, however, is the increased number of abnormal platelets of the giant variety, many of them being larger than 25 μ. These platelets may well be too large to pass through many of the capillaries and because of their size produce small thrombi.

THESE cases, when compared to those described by Dr. Mayo in 1928, appear to answer the problem which he posed. Since many of them have a return of the blood findings to a relatively normal level, the indication is that hypersplenism, together with infarction of the spleen, as a result of chronic lymphocytic or granulocytic leukemia, so distorts the peripheral blood picture because of cell destruction and absorption of leukopoietic substance from splenic infarcts as to appear as an acute exacerbation of the underlying disease.

At the present time, armed with the tools not available 25 years ago, splenectomy may be performed without subjecting the patient to any great degree of risk. Adequate blood must be available when needed, and anticoagulants should be a routine procedure in the postoperative period following splenectomy for hypersplenism in chronic granulocytic leukemia. The more recently used control drugs should be used wherever deemed advisable to control any excessive leukocyte rise.

CONCLUSIONS

Splenectomy as a modality of therapy in leukemia cannot be used lightly and should be considered a final control measure after all other forms of therapy have been discarded. Certainly, the spleen performs an excellent function in reducing the leukocytic count in both granulocytic and lymphocytic leukemias. For this reason, if no other, splenectomy should be restricted to those cases in which hypersplenism is so severe that maintenance of a normal red cell count is impossible. Splenectomy may then be resorted to with good results.

The selection of cases should fit into a common pattern; the red cell count should be falling, and the transfusion test should be clearly positive. A falling leukocyte count or a rising leukocyte count may be associated with this situation. Where there is a splenic neutropenia, a falling leukocyte count may exist, whereas in infarction an elevation of immature leukocytes may be noted. Platelets will frequently be reduced. Splenectomy should be performed, however, before the platelet count is reduced to a dangerous level. The bone marrow will vary according to the type of leukemia; in granulocytic leukemias in most instances all cells will be hyperplastic. Splenectomy may be warranted—as in case 2—in spite of a hypoplastic marrow where there is evidence of excessive splenic destruction of cells. The stool urobilinogen must be elevated. This test should be performed on several 24-hour specimens. Fever may or may not be a symptom but is frequently noted in the granulocytic leukemias as the result of infarction. With these findings present, consideration should be given to splenectomy. Delay, when the platelet count is falling, may result in excessive bleeding tendency which will result in the patient being a poor operative risk because of excessive bleeding tendency.

SUMMARY

From our experience with splenectomy in these cases of leukemia we believe consideration should be given to the procedure as a measure to prolong the life of leukemia patients. When hypersplenism presents itself as a formidable problem and red cell destruction is excessive, splenectomy should be resorted to.

Splenic infarction may cause an increase in activity of the leukemia. Platelets and white cells may also be decreased as part of the hypersplenic picture. Splenectomy for these features alone has not been encouraging.

Anticoagulants should be used for prolonged periods in granulocytic leukemias to reduce chronic thromboses.

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Meckel's Diverticulum as the Source of Massive Intestinal Hemorrhage

FRED R. SANDERSON[1] AND FRANCIS A. BARRETT, JR.[2]

GEORGETOWN UNIVERSITY MEDICAL CENTER, WASHINGTON, D. C.

THE pathologic conditions which occur in Meckel's diverticulum have been classified by Greenblatt, et al.,[8] into several groups: (1) the peptic group in which gastric mucosa exists with or without ulceration and in which hemorrhage or perforation may occur; (2) the inflammatory or diverticulitis group in which acute inflammatory changes take place, some resulting in perforation and gangrene; (3) the obstructive group in which intestinal obstruction results from intussusception, volvulus or adhesions and bands; (4) the tumor group which includes both benign and malignant growths as well as cysts and heterotopic tissue, and (5) the umbilical group which includes fecal fistulas and cysts.

This study is based on the surgical records of 5 cases of the peptic group, in which massive intestinal hemorrhage is the predominant symptom observed.

CASE REPORTS

Case 1—The patient, a 14-month-old white female, had an episode of intestinal bleeding at the age of nine months. A gastrointestinal series at that time was negative. The baby remained in good health for the next five months, when again there was an episode of intestinal bleeding which had persisted for four days before the child was brought to the hospital. The child was listless and had fainted. The hemoglobin was 34 per cent and the red blood cells numbered 1,800,000. A total of 600 cc. of blood was given in the next 48 hours and an exploration advised for either a Meckel's diverticulum or a polyp of the colon.

At operation a large, broad-based Meckel's diverticulum, 1½ by ¾ inches, was excised through an elliptical incision in the ileum, including a ½ inch margin around the base. The incision was closed obliquely. Recovery was uneventful. The pathologist reported a Meckel's diverticulum with gastric and ileal mucosa and ulcers in each, one at the base and one at the tip.

Case 2—The patient, a 5-month-old white infant, began to have profuse rectal bleeding 30 hours before admission to the hospital in a state of shock. The hemoglobin was 15 per cent, the red blood cells numbered 1,550,000. Three hundred cubic centimeters of whole blood were given, bringing the hemoglobin to 77 per cent, the red blood cells to 4,200,000. A diagnosis of bleeding Meckel's diverticulum was made, and surgery was performed three hours after admission. A Meckel's diverticulum, 2 cm. in length and 1.5 cm. in diameter, was excised from the ileum, 18 cm. from the ileocecal valve. An ulcer in gastric mucosa was found near the base. The patient made a good recovery.

Case 3—The patient, a 40-year-old white male, was admitted to the hospital after he had vomited blood. He had noted slight lower abdominal pain the day before which was followed by vomitus of bright red blood. The patient fainted, but later felt better. His stools became black following this episode. On admission his blood pressure was 80/44, his pulse rate 110 per minute. The hemoglobin level was 37 per cent, the red blood cell count 2,100,000.

In the next ten-day period, the patient vomited bright red blood on two occasions and continued to pass tarry stools. He was given 5,000 cc. of whole blood during this period. On the evening of the eleventh day the patient went into shock, the hemoglobin fell to 17 per cent, the red blood cell count to 1,550,000, and 3,500 cc. of blood were required to save his life. A diagnosis of bleeding peptic ulcer was made and an exploration was done. The stomach was opened, but no ulcer found. The duodenum was normal. A Meckel's diverticulum, 3 by 2 by 1 cm. was found 18 cm. from the ileocecal valve, and was excised. It contained gastric mucosa and a group of aberrant ducts, located beneath the muscularis. No definite ulceration was found. The patient's recovery was uneventful.

Case 4—The patient, a 51-year-old male physician, had complained of vague abdominal pains for fifteen years. On the morning of admission to the hospital he became weak, passed a large tarry stool, and went into mild shock. The hemoglobin was 67 per cent and the

[1]Professor of Surgery, Emeritus, Department of Surgery, Georgetown University Medical Center, Washington, D. C.

[2]Resident in Surgery, Providence Hospital, Washington, D. C.

red blood cells numbered 3,570,000. During the next three days he passed several tarry stools and was given 1,000 cc. of blood. The bleeding stopped and he was discharged on the seventh day. A gastrointestinal series disclosed a duodenal ulcer.

Two years and three months later he was re-admitted to the hospital for weakness and tarry stools, with a hemoglobin of 34 per cent and red blood cell count of 1,770,000. The bloody stools persisted for four days and during the course of the next ten days he received 2,500 cc. of blood.

Several months later a gastrointestinal study was done at the Mayo Clinic which showed duodenal ulcer and a large Meckel's diverticulum with an ulcer in the base. Some months after returning home and with practically no abdominal symptoms present, an exploration was done. A long adherent appendix was removed. A large Meckel's diverticulum, measuring 15 cm. in length and 2 cm. in diameter, was found 18 inches above the ileocecal valve. The tip was attached to the umbilicus and there was a mesentery throughout its whole length. Excision was done through an incision transverse to the long axis of the ileum. The stomach and duodenum were not explored as the McBurney incision was inadequate. Convalescence was stormy. Intestinal obstruction developed, for which an enterostomy was done on the fourth postoperative day. Six days later the patient eviscerated, requiring a re-suture of the wound. After two and one-half years there has been no further bleeding and the digestive symptoms have disappeared. Pathologic examination disclosed a large Meckel's diverticulum with ectopic gastric mucosa.

Case 5—The patient was a 28-year-old female, with a history of passing tarry stools eleven months before. A gastrointestinal series revealed duodenal ulcer. She was placed on an ulcer regimen, but continued to complain of vague abdominal distress. For three days prior to admission to the hospital she passed both red and dark jelly-like stools, and became extremely weak and faint. Hemoglobin was 5.2 gm. or 35 per cent on admission to the hospital. On the first day she received 2,000 cc. of blood. She vomited frequently and passed red, bloody stools. She received 2,000 cc. more blood on the second day, as rectal bleeding persisted. On the third day she complained of crampy pain in the lower abdomen, with mild tenderness on pressure. A diagnosis of bleeding duodenal ulcer was made and she was operated upon the same day.

There was no evidence of duodenal or gastric ulcer. About two feet from the ileocecal valve a large Meckel's diverticulum was found and resected. The patient made an uneventful recovery. Pathologic examination revealed a Meckel's diverticulum, 2.5 cm. in length and 2 cm. in circumference. No definite ulceration was found but a pinpoint size hemorrhagic nodule was found at the junction of the ileal and gastric mucosa of the diverticulum. At the tip of the diverticulum a pale, firm nodule measuring 1 by 1 by 0.5 cm., grossly resembling pancreatic tissue, was found buried in normal appearing mesenteric fat. Microscopic examination showed the continuity of the mucosa broken by a minute ulceration in an area at the junction of the bowel mucosa with that of the gastric mucosa of the diverticulum, beneath which there was marked inflammatory reaction. A section through the nodule showed normal, functioning pancreatic tissue. Pathologic diagnosis was Meckel's diverticulum, with minute ulceration in gastric mucosa and heterotopic pancreatic tissue.

JOHANN Frederick Meckel in 1815 described an anomaly of the terminal ileum in the form of a diverticulum, which he associated with the omphalomesenteric or vitelline duct. It occurs in 1 to 3 per cent of all persons. Brown and Pemberton[3] stated that Carlson, from the study of Meckel's diverticulum taken from the necropsy data at the Mayo Clinic for a period of ten years, confirmed the usual incidence of 2 per cent with males predominating 2 to 1. Conrad[5] reported 13 cases in 2,050 postmortem examinations at the New York Hospital and quoted Christie who found 63 cases or 1.1 per cent in 5,768 postmortems at Babies Hospital. It is well established that the anomaly occurs more frequently in males than in females.

Anatomically the diverticulum is found in the terminal ileum, 15 to 100 cm. from the ileocecal valve. It varies in size from a small nubbin or outpouching to giant size, that of Moll's[16] case measuring 33½ inches. Some are attached to the umbilicus, while usually the diverticulum lies free within the peritoneal cavity. Occasionally there is a mesentery. The diverticulum in case 4 measured 15 cm. in length, the lumen was the size of the ileum, and there was a mesentery throughout its length. The tip was attached to the umbilicus. The sizes of the diverticula in the remaining cases were average, measuring from 3 by 2 by 1 cm. to 2 by 1½ by 1 cm.

Early in fetal life the omphalomesenteric duct, which connects the intestine with the yoke sac, normally atrophies and disappears. When there is an arrest of the retrogression and obliteration is not complete, the blind pouch remains, forming Meckel's diverticulum. If the diverticulum is attached to the umbilicus and remains open after birth, a fecal fistula results. A fistula develops when the intestinal end closes and the umbilical end remains open. When both ends are closed and the diverticulum fails to obliterate, a cyst develops. A history of any one of these conditions in a child or adult presenting a picture of an acute abdomen or intestinal hemorrhage should immediately prompt one to consider Meckel's diverticulum as the probable cause.

Heterotopic tissue in Meckel's diverticulum is found in 15 to 25 per cent of all diverticula.[3, 8, 15]

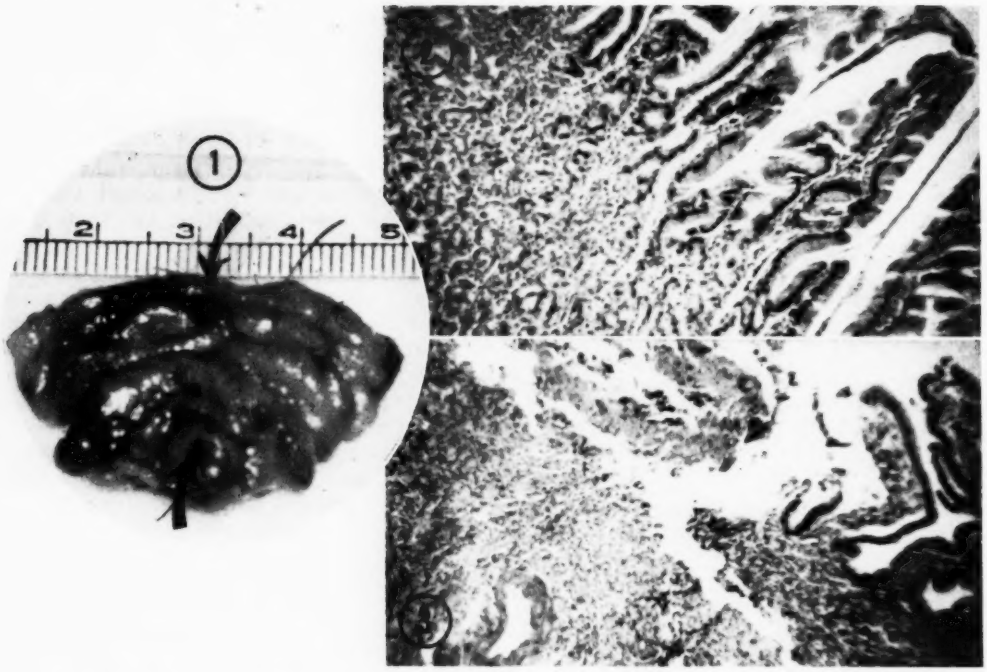


FIGURE 1 *(Case 1)*. Photograph of Meckel's diverticulum showing two ulcers as indicated by the arrows. The one at the top occurred in gastric mucosa while the one in the base was in ileal mucosa.

FIGURE 2 *(Case 1)*. Low power photomicrograph showing heterotopic gastric mucosa.

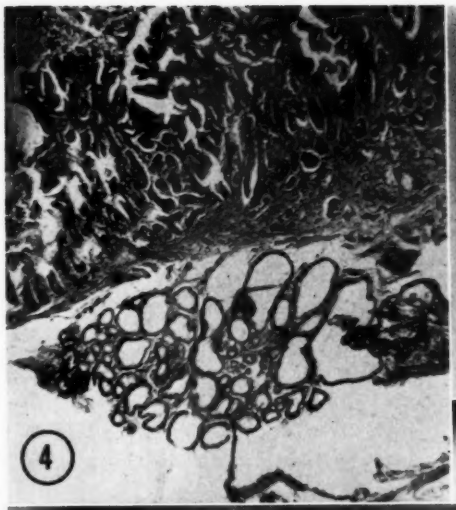
FIGURE 3 *(Case 1)*. Low power photomicrograph showing ulceration of the ileal mucosa.

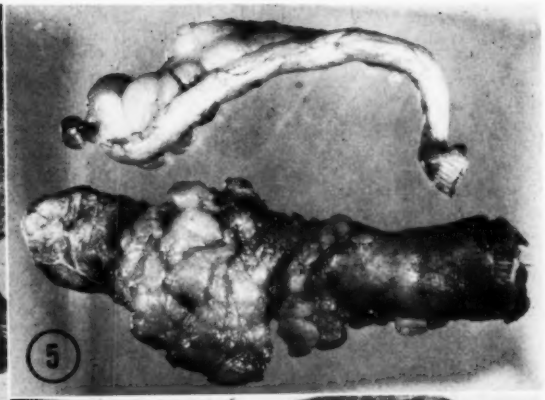
Of those cases producing symptoms, the incidence rises to 60 to 75 per cent.[9] The most common tissue found is gastric mucosa and this is followed in incidence by duodenal and pancreatic tissue. Wilkinson[18] figured the possibility of gastric epithelium to be roughly 1 in every 170 persons. Gastric mucosa was present in all the cases in this study and in case 5 both pancreatic tissue and gastric mucosa were found. The rarity of cases of both pancreatic and gastric heterotopea in proved Meckel's diverticulum is revealed by Bigelow and Clark[2] who were able to find only 8 cases. In the same article they collected 30 cases beside their own of pancreatic heterotopia in proved Meckel's diverticulum.

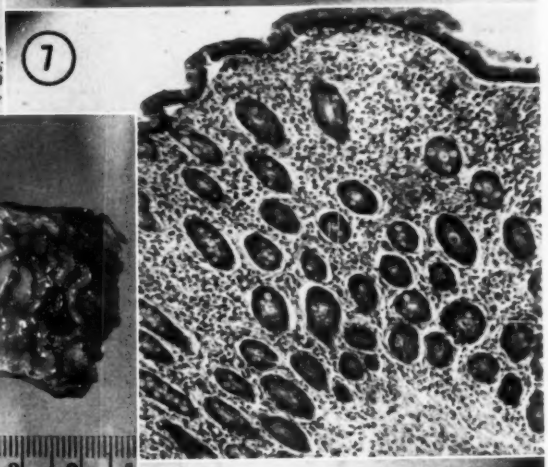
The most acceptable theory which accounts for the presence of heterotopic tissues, such as gastric mucosa and pancreatic tissue, in Meckel's diverticulum, is advanced by Greenblatt, et al.,[8] who believe that the vitelline duct has some slight function in early fetal life, associated with digestion and that the endodermal cells lining the primitive intestinal tube possess the potentiality of developing into any glandular elements of the fully developed gastrointestinal tract. As soon as the digestive function ends in early fetal life, retrogression normally takes place, with complete obliteration and disappearance of the duct. Occasionally, due to retarded embryologic retrogression of the duct, a vestige of heterotopic tissue remains. Their theory is known as that of dysembryoma.

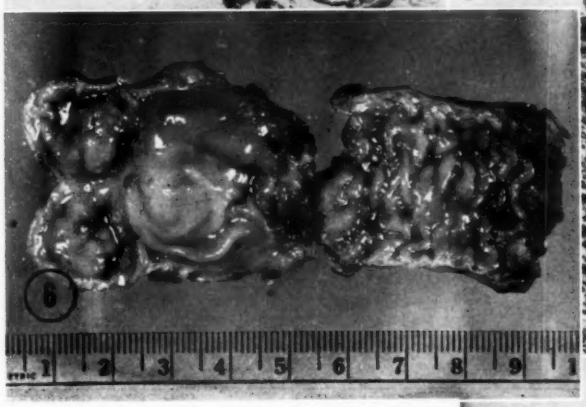
The presence of gastric mucosa, capable of secreting gastric juice as established by Hudson[10] in 1933, may result in erosion or ulceration with the production of a definite peptic ulcer, capable of bleeding and of perforating. Deetz,[7] in 1907, is credited with the first report of the peptic nature of the ulceration. Callender,[4] in 1915, reported a death from intestinal hemorrhage in an infant 19 months old, which at autopsy revealed a punched out ulcer at the base of a Meckel's diverticulum over an eroded vessel.

In 1924, R. H. Jackson[13] reported a case of









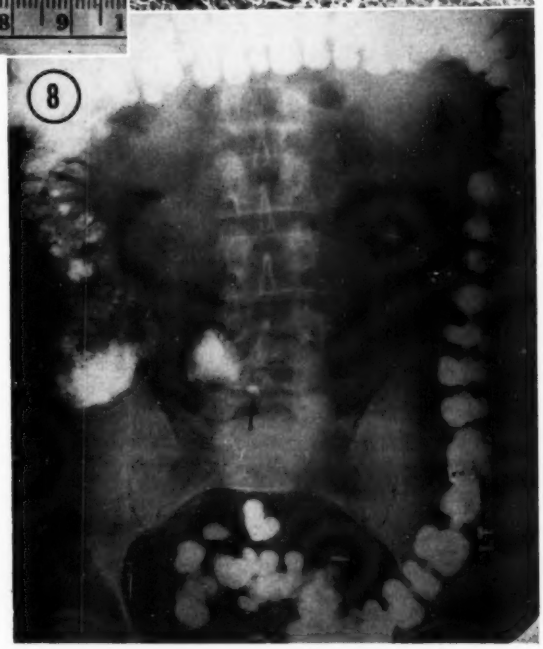


FIGURE 4 *(Case 3)* Low power photomicrograph of Meckel's diverticulum showing heterotopic gastric mucosa and glands of probable pancreatic origin.

FIGURE 5 *(Case 4)*. Photograph of Meckel's diverticulum and appendix removed, showing large size of the diverticulum.

FIGURE 6 *(Case 4)*. Photograph of opened Meckel's diverticulum, showing gastric mucosa in proximal half.

FIGURE 7 *(Case 4)*. Low power photomicrograph of heterotopic gastric mucosa found in Meckel's diverticulum.

FIGURE 8 *(Case 4)*. Roentgenogram showing the Meckel's diverticulum taken at the Mayo Clinic eighteen hours after opaque meal was administered. The small fleck of barium toward which the arrow is pointing probably represents an ulcer near the neck of the diverticulum. A roentgenogram taken three hours after opaque meal showed a similar picture.

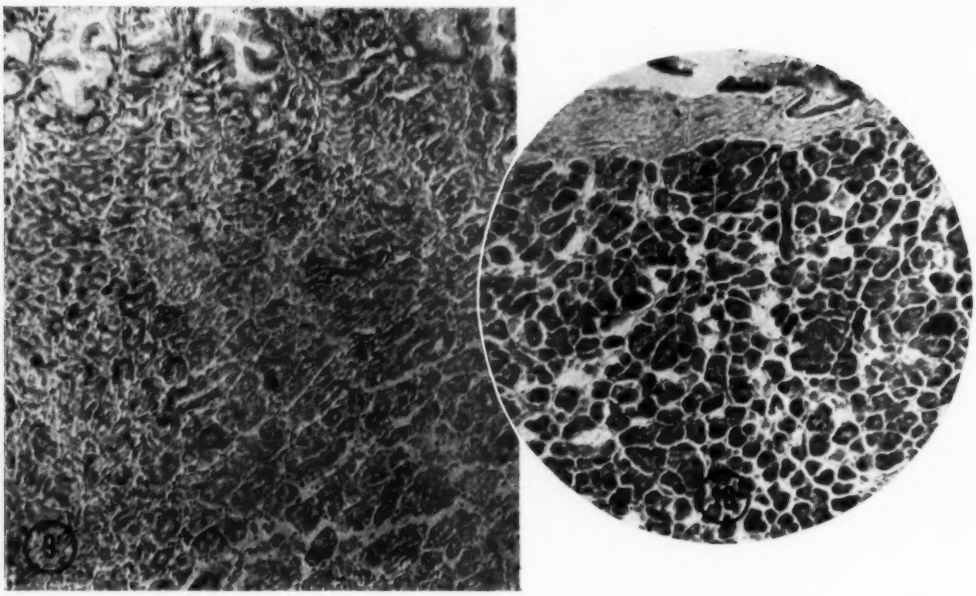


FIGURE 9 *(Case 5)*. Low power photomicrograph of Meckel's diverticulum showing heterotopic gastric mucosa.

FIGURE 10 *(Case 5)*. Low power photomicrograph of nodule found in tip of diverticulum showing pancreatic tissue.

repeated intestinal hemorrhage in a boy 10 years old, who was operated on in 1912 and an eroded vessel was found in a marginal ulcer, thought to be tuberculous, but there was no microscopic examination.

Arnold Jackson[12] stated that he reported, in 1926, the first acute case of intestinal hemorrhage due to an ulcer in a Meckel's diverticulum.

Abrams,[1] in 1938, brought out the fact that there may be hemorrhage from Meckel's diverticulum without demonstrable ulceration. The diverticulum removed in case 3 revealed no ulceration to account for the severe bleeding.

In case 4, the acute massive bleeding had occurred six months previous to operation and pathologic examination disclosed no evidence of erosion or ulceration or scarring from a healed deeper ulcer. Johnston and Renner[14] believed that in some of the cases they collected in which ulcers were not found, the ulcer or erosion may have been so superficial that it was overlooked, or the ulcer may have healed before operation, or the ulcer may have been located in the ileum where it was not seen.

When ulceration occurs it is usually in the base at the junction of the intestinal and gastric mucosa and has been compared by several to the marginal ulcer which develops after gastroenterostomy or gastrojejunostomy. The tip may occasionally be the site of the ulceration.

The ulcer may be superficial or may involve the deeper layers of the diverticulum. Massive hemorrhage may occur from a superficial erosion as found in case 5. Johnston and Renner,[14] and Hudson[10] have had similar cases. In cases 1 and 2, the ulcerations were of the typical peptic type. Occasionally there may be two ulcers, as seen in case 1—one located in the ileum, the other in the gastric mucosa. Coexisting duodenal ulcer may occur as in case 4, where the diagnosis was made by x-ray examination but not confirmed at operation as the duodenum was not explored.

Although there is a great variance in the ages of peptic ulcer cases, the greatest number are in male patients under 20 years of age. Johnston and Renner,[14] in reviewing 62 definite ulcer cases, found the ages to vary from 5 months to 45 years, with the preponderance in infants and children. Eighty-four per cent of their reported cases were under 16 years of age, while the greatest number were between 1 and 10.

AGES OF FIVE CASES REPORTED

Case 1	14 months
Case 2	5 months
Case 3	40 years
Case 4	51 years
Case 5	28 years

Of these cases, 2 were females and 3 were males.

The outstanding symptom is intestinal hemorrhage, usually severe and exsanguinating. The passed blood is usually red and fresh, but may be tarry—or there may be a combination of the two. Case 3 vomited blood at the onset, followed by the passage of tarry stools. In reviewing the literature, this is the only case in which there was vomited blood from a bleeding Meckel's diverticulum. Associated with the hemorrhage are pallor, weakness, and even syncope, as in case 2. The hemoglobin may fall rapidly, or it may take several days before extreme anemia ensues. In cases 2 and 3, the hemoglobin fell to the low figure of 15 and 17 per cent respectively. If perforation does not occur, the bleeding may stop and the patient may go for months or years before there is a recurrence.

Crampy abdominal pain may appear before or after the intestinal bleeding, but is not a constant finding. In those cases complicated by perforation and peritonitis or intestinal obstruction from bands, intussusception or volvulus, pain is the predominant symptom.

THE diagnosis should not be confusing in those cases of severe hemorrhage in the young individual or infant who has a normal past history. In the older patients, who have had some digestive distress in the past, the diagnosis of bleeding duodenal ulcer is a frequent and plausible mistake. Intestinal polyp is suggested frequently as the cause of the bleeding but it is most unusual for a polyp to produce massive hemorrhage.

There should be no confusion with the blood dyscrasias, as the blood picture is that of an acute secondary anemia, with normal bleeding and clotting time. The x-ray is of little assistance in making the diagnosis, as the diverticulum rarely shows in the picture. There are 2 cases on record in which the diverticulum was demonstrated by the x-ray—one by Cole and Pfahler as reported by Vastine[17] and the other by Hudson and Koplik.[11] The demonstration of Meckel's diverticulum by x-ray was accomplished in case 4 at the Mayo Clinic, and, in addition, a peptic ulcer can probably be viewed in the base of the diverticulum. I am indebted to the Mayo Clinic for granting me the privilege of using their x-ray film, which is reproduced in Figure 8. The same gastrointestinal study also showed a deformed duodenum which was interpreted to be a duodenal ulcer.

Surgical exploration and resection of the diverticulum is the treatment of this condition, as soon as the loss of blood has been replaced by transfusions. It is hazardous to observe these cases for too long a period, as perforation has occurred in several cases in the hospital. Resection of the diverticulum transversely or obliquely to the long axis of the cecum allows removal of a small cuff of ileal tissue without encroachment upon the lumen of the bowel. In some cases in which the ulceration is located at the base of the diverticulum or in the adjacent cecal mucosa, segmental resection of the ileum and end-to-end anastomosis should be done. Recovery is usually rapid and the mortality is low. There were no deaths in this small series. If perforation occurs, the mortality is over 50 per cent, as reported by Johnston and Renner.[14]

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Pulmonary Function Studies in Surgery

JOHN J. CURRY AND FRANK S. ASHBURN*

GEORGETOWN UNIVERSITY MEDICAL CENTER, WASHINGTON, D. C.

With the increase in major surgical procedures in elderly patients a greater need has arisen for measurements of pulmonary function and estimation of pulmonary reserve. In vigorous patients such tests are of little practical value. On the other hand, when the patient is a poor surgical risk, has extensive pulmonary disease (fibrosis or emphysema, for example), and is on the borderline of pulmonary insufficiency, such tests are of paramount importance. Thus the decision to operate may be tempered by the results of testing the patient's pulmonary function and the choice of operative procedure may be dictated, in part at least, by the results of these tests.

Moreover, advances in surgery of the chest have doubled the indications for thoracic operations in individuals already embarrassed by reduction in pulmonary reserve. In these cases determination of the function of the individual lung or parts of the lung is a necessity.

The purpose of this report is to outline a few simple tests of pulmonary function which are readily available and relatively easily performed and relate them to general and thoracic surgery. Unfortunately some of these tests are subject to wide variations even in normal individuals. When they are considered as a group, however, and their limitations known, much valuable information of pulmonary function may be gained.

Following the reports of Cournand and Richards,[1] Riley[2] and others, great interest was aroused in bronchospirometry and in the problem of determining pulmonary function. Unfortunately this general interest has not been sustained and now procedures originally advocated are carried out in the relatively few large centers primarily devoted to this subject. The apparatus required generally was designed by the authors themselves and appears to be too complicated for most chest physicians and surgeons. Furthermore detailed knowledge of the procedures and their underlying physiologic basis is required and the time needed for such studies is frequently discouraging. We are indebted to Waring[3] for emphasizing the simpler, practical tests of pulmonary function which can give such valuable information in those patients with impaired lung function.

Pulmonary function has been divided into two phases: the ventilatory phase is concerned with all those mechanisms by which air is moved into and out of the lungs while the respiratory phase is concerned with the gaseous exchange between the blood and the air. Insufficient ventilation results in dyspnea whereas impairment of gas exchange leads to hypoxia and cyanosis.

VENTILATORY FUNCTION MEASUREMENTS

We employ a machine which resembles a Benedict-Roth metabolism apparatus except that the tank has a 9 liter capacity.* The soda lime container and directional values are removed to decrease the resistance of the circuit. A record of ventilation is traced in ink on plain white paper on a motor-driven drum revolving at a speed of either 3 or 15 minutes per revolution. In the majority of studies, the more rapid speed

*From the Departments of Medicine and Surgery, Georgetown University Medical School and Georgetown University Hospital.

*Manufactured by Warren E. Colline, Inc., Boston, Massachusetts.

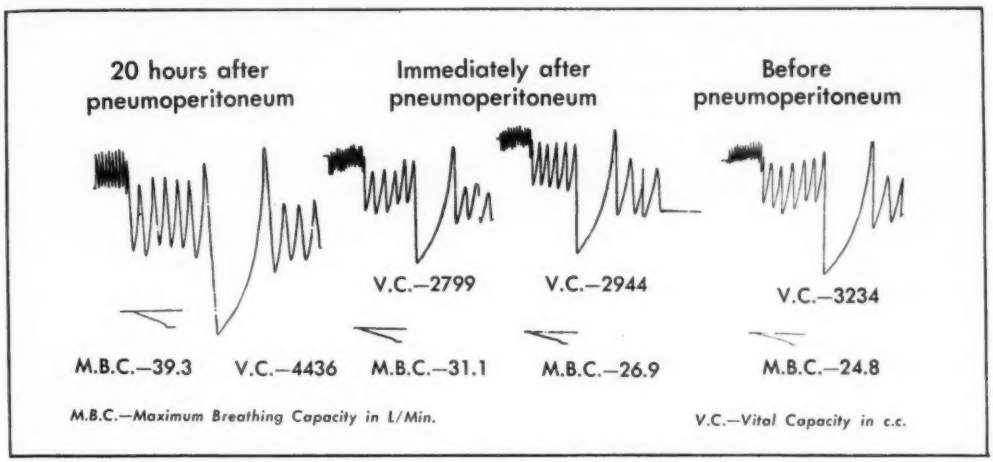

FIGURE 1. Pulmonary function studies in a 43-year-old patient with emphysema.

is employed. Since each centimeter of excursion of the pen is equivalent to 207.3 ml. of air, tables may be constructed for rapid conversion of the measurements to milliliters of air. To facilitate measurement of the maximum breathing capacity there is an attachment which measures inspiration only and reduces the excursion 25 times.[4] Tables may also be constructed for direct reading of the maximum breathing capacity in milliliters of air. If precise measurements of time are wanted, a signal magnet should be attached since there is a slight variability of speed depending on the size and tightness of the roll of record paper. This machine may also be used for measurement of basal metabolism which increases its functional use in the clinic.

The subject is comfortably seated and after a rest and explanation of the tests, the tank is half filled with room air and the patient connected to it by a rubber mouth piece. A nose clip is applied and after a short period of adjustment to the artificial type of breathing, the valve is turned so that the patient breathes in and out of the tank. When several ordinary respirations are drawn, the greatest possible inspiration and expiration are made for recording the vital capacity. Since the vital capacity is recorded on a moving drum, there is also opportunity for measuring the vital capacity exhalation time. A few ordinary respirations are again recorded and at the completion of a normal expiration the patient is instructed to breathe out as much more air as he can, thus giving a measurement of the reserve air.[5] Several more ordinary respirations are then drawn and the patient is told to breathe in and out as deeply and as rapidly as is comfortably possible for a period of 15 to 20 seconds. When the test appears to be exhausting, the shorter time is employed although this increases the variability of the results. Thus the maximum breathing capacity is recorded and calculated in liters per minute.

After each set of tests the tank is flushed with room air five times to prevent the accumulation of carbon dioxide.

VITAL CAPACITY TESTS

Measurement of the vital capacity is without doubt one of the most widely used tests of pulmonary ventilation. It has become increasingly clear, however, that there is no consistent relationship between the vital capacity and dyspnea. We have studied a great number of individuals with normal or near normal vital capacities and yet notable shortness of breath. This is well shown in the following case.

Patient A. M., a 43-year-old male with emphysema, was given a pneumoperitoneum with 1000 ml. of air (Figure 1). Within 24 hours the vital capacity had increased from 3234 ml. to 4435 ml. and yet the patient was only slightly improved clinically. On the other hand the maximum breathing capacity showed only little

improvement, measuring 24.8 liters per minute prior to pneumoperitoneum and 39.3 liters per minute after therapy. This shows not only dyspnea in the presence of a normal vital capacity, but also that a notable increase in vital capacity is not always associated with comparable improvement in breathing. This deficiency of the vital capacity is partly overcome by noting the time consumed with the curve of expiration. Normally expiration of the vital capacity consumes but a few seconds whereas in emphysema 10 seconds or more are frequently required for full expiration. This case also illustrates that the marked prolongation of vital capacity slope is comparable with the reduction in maximum breathing capacity.

In our experience in patients with emphysema there has been a close correlation between the amount of time needed for expiration, shortness of breath and the maximum breathing capacity. Recording the slope of expiration on a moving drum also affords a check on the cooperation of the patients since the slopes of successive tests should be similar.

RESERVE AIR

Christie has shown that recording the reserve air separately is of importance since by comparison with the reserve air as computed from the vital capacity it may represent the earliest sign of pulmonary impairment. In emphysema the reserve air computed from the vital capacity slope is much less than the reserve air determined as a separate function.

MAXIMUM BREATHING CAPACITY

Cournand, Richards, and their associates have pointed out that dyspnea is more closely related to reduction in maximum breathing capacity (MBC) than to vital capacity.

Several methods are available for measuring the maximum breathing capacity, but that in which the subject chooses his own rate and depth of respiration gives the most reproducible results. Gray and Green[6] in 89 healthy aviation cadets obtained a mean value of 168 liters a minute with a standard deviation of plus or minus 22 liters a minute. The ventilation capacity was correlated with surface area but not with age or height and weight separately.

We find a variable normal range approximating 150 liters a minute for males and 100 liters a minute for females. These figures agree with those noted by Cournand and Richards.

Since deep and rapid breathing sometimes induces coughing in subjects with bronchial infection, difficulty occasionally arises in obtaining a record. In these cases we have the subjects breathe more rapidly and less deeply. In subsequent tests in the same individuals care is taken to perform the tests in a similar fashion.

It has been our custom to discount tests made while the patient is learning the technic. An average is then made of three determinations to obtain the resting level. On some occasions, however, particularly in emphysema, the first determination may be the largest obtained. In this case we consider the value in determining the average.

RESPIRATORY FUNCTION

Cournand and Richards[1] have concisely described the factors leading to respiratory insufficiency. The ventilation of enlarged, nonfunctioning alveoli, as in emphysema, is of serious consequence to the economy of respiration. The partial pressures of respiratory gases and the condition of the semipermeable membrane barrier between the alveolar air and the blood are also important. It should be noted that exercise is very helpful in unmasking defects in respiratory gas exchange.

Alveolar ventilation may be measured by collecting samples of gas in the Douglas bag under basal conditions and with exercise and measuring in the Haldane apparatus the oxygen removed and the carbon dioxide eliminated. The rate of oxygen uptake per hundred milliliters of gas ventilated during exercise is a valuable index of alveolar ventilation.

Determination of the arterial oxygen saturation and carbon dioxide tension are helpful in indicating the level of respiratory insufficiency.

PULMONARY CIRCULATORY MEASUREMENTS

Some indication of the role of congestive failure in producing dyspnea may be gained by determination of the circulation time, venous pressure, and the effects of saline infusion.

Many substances have been proposed and used for measuring the circulation time.[7] We have found calcium gluconate a reliable test agent. With a 19 gauge needle 4 cc. of a 20 per

cent solution of calcium gluconate is injected rapidly in an antecubital vein. The interval between the beginning of injection and the appearance of a hot sensation in the mouth and face is the circulation time. In congestive failure the time usually exceeds 20 seconds.

It has been stated that calcium gluconate should be used cautiously in the digitalized patient but we have never experienced any difficulty with the drug.

Venous pressure may be measured by direct methods.[8, 9] In one method with the subject resting in bed a 19 gauge needle, connected by a Y tube with a reservoir of physiologic saline and a sterile manometer tube of 2 mm. bore, is inserted in an antecubital vein. The arm is abducted and placed in a comfortable position. The zero point of the manometer is set 100 mm. above the level of the back. Saline is allowed to run into the vein and readings are made on the manometer until a steady level is reached. In another method use is made of a phlebomanometer as described by Winsor and Burch.[9] The normal range of venous pressure is between 30 and 100 mm. of water.

A temporary increase in blood volume may be brought about by infusion of 1500 cc. of normal saline during a period of 30 minutes and the vital capacity, venous pressure and circulation time are measured before and after the infusion.[10, 11] A decrease in vital capacity of over 5 per cent, a rise in venous pressure to a level over 100 mm. of water, or a prolongation of the circulation time of over 5 seconds are considered abnormal and suggestive of pulmonary congestion.

APPLICATION OF VENTILATION TESTS TO GENERAL SURGERY

When surgery is contemplated in any subject with embarrassed respiration, there is a need for pulmonary function studies to ascertain the extent of the difficulty. These subjects do not tolerate any additional drug, reflex or mechanically induced bronchospasm, or further interference with the bellows action of the chest.

In the pre-operative period it is well to avoid drugs such as barbiturates and morphine which tend to promote bronchospasm and rather to use scopolamine and Demerol. The latter drugs are not only sedative and analgesic but produce bronchodilation as well.[12]

Codeine should be prescribed sparingly since it tends to depress the cough reflex. Similarly, cyclopropane which promotes bronchospasm should be avoided as the anesthetic agent.

Operations which call for a transthoracic approach which may be followed by pleural effusion or operations which result in splinting of the diaphragm should be undertaken with caution in patients with a maximum breathing capacity of less than 60 liters per minute.

In the postoperative period atelectasis and pulmonary embolism may have much more serious consequences and hence every precaution should be taken to prevent these complications. The use of the Trendelenburg position and upper abdominal binders which splint the lower costal cage are to be avoided because they promote further respiratory embarrassment.

In patients with reduction in pulmonary function tests an evaluation of the effect of various sympathomimetic amines, antihistaminic agents and anticholinergic agents may be made pre-operatively by checking improvement in the tests after the administration of the various medications.[13] In this manner one can determine pre-operatively the agents best suited to relieve dyspnea in the postoperative period.

APPLICATION OF VENTILATION TESTS TO THORACIC SURGERY

It is important that the patient who undergoes resection of a lung or a part of a lung does not become a pulmonary cripple. It must be determined pre-operatively whether or not the patient has sufficient breathing reserve to tolerate the procedure. Following operation the patient's maximum breathing capacity must be no less than 30 liters per minute if he is to be free of dyspnea.

When the pre-operative maximum breathing capacity is high the reserve is obviously adequate. When the maximum breathing capacity is reduced, the removal of a poorly functioning lung or lobe will be well tolerated. In such instances the surgeon operates with assurance. Where on the other hand the pre-operative maximum breathing capacity approaches 30 liters per minute, extirpative pulmonary surgical procedures had best not be done.

PULMONARY RESECTION

Following pulmonary resection the simple determination of MBC can serve as an index as

to the necessity of additional thoracoplasty to prevent overdistention of the remaining pulmonary tissue. Evidence is constantly accumulating to show that such thoracoplasty is not invariably necessary and this fact makes the repeated determination of pulmonary function by a simple means a necessary part of the postoperative follow-up in these cases.

The problem of post resection thoracoplasty in cases of pulmonary tuberculosis is entirely different and need not be discussed here.

THORACOPLASTY

Thoracoplasty, used therapeutically in cases of pulmonary tuberculosis, at first glance would seem invariably to reduce the patient's ventilatory function. Such is not the case and, in fact, even increases in MBC have been noted following the judicious use of thoracoplasty.

As in the case of pulmonary resection, thoracoplasty is an irreversible procedure and it is imperative that it be known whether or not the patient has sufficient breathing reserve to tolerate the procedure. Once again the patient with a high or nearly normal MBC constitutes no problem even though the contemplated thoracoplasty is to be quite extensive. If the poorly functioning side is to be collapsed it is still possible to do a thoracoplasty without danger of pulmonary decompensation even if the preoperative MBC is moderately reduced.

The side of better function may be subjected to collapse, even in the presence of moderately severely lowered MBC if the operation is limited strictly to give a highly selective collapse. In this connection it is interesting to note that Wright has found no change or an improvement in MBC following selective apical collapse by thoracoplasty.

PNEUMOTHORAX

Rare is the need for intensive investigation of pulmonary function in cases of pneumothorax. The studies are interesting but rarely is it essential to have such data for the proper management of pneumothorax.

EXTRAPLEURAL PNEUMOTHORAX

Gaensler has shown MBC is usually increased following selective collapse of the diseased lung by extrapleural pneumothorax or lucite plumbage. When a decrease in MBC accompanies this procedure, it is less than that following pneumonectomy, lobectomy, thoracoplasty or intrapleural pneumothorax. The loss in function is less than that following phrenemphraxis and usually less than that accompanying pneumoperitoneum.

PHRENEMPHRAXIS

The MBC is usually lowered from 10 to 15 liters per minute by temporary interruption of the function of one phrenic nerve. Therefore this procedure can be expected to be well tolerated if the patient has an MBC of 50 liters per minute or more. If the better functioning side is to have phrenic paralysis and the MBC approaches 50 liters per minute, pulmonary decompensation and constant dyspnea may result.

PNEUMOPERITONEUM

Pneumoperitoneum rarely reduces MBC more than 5 liters. In the case of severe emphysema cited above slight increase in MBC was noted. Almost never will MBC be reduced enough by pneumoperitoneum to contraindicate the procedure, either when used alone or in conjunction with interruption of the phrenic nerve.

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Polyps of the Large Bowel

C. EDWIN McNAMARA*

GEORGETOWN UNIVERSITY MEDICAL CENTER, WASHINGTON, D. C.

Polyps, present in the colon and rectum, are a grave threat to the immediate health and the future life expectancy of the individual who is unfortunate enough to develop them. With the recognition, among the medical profession, of the importance of proctoscopic examinations and improvements in roentgenologic technics, they are being diagnosed with increasing frequency. Armed with the modern powerful chemotherapeutic and antibiotic agents, plus an increasing knowledge of bodily fluid and chemical balance, the surgeon is performing more definitive operations aimed at the elimination of these lesions.

With these thoughts in mind, it is well to review the current literature in order to keep abreast of the present opinion as regards such a common and serious disease entity. It is most interesting in such a review to find writers from widely diverse sections of the country reaching the same conclusions. It, also, is very stimulating to find them using the various journals as a debating platform for discussion of their points of disagreement.

A paper by Menzel, in 1721, is believed to be the first description of polyps of the large bowel. This work was on postmortem specimens, of course. Cripps, in 1882, is thought to be the first to call attention to the familial type. The years after 1900 have produced an increasing volume of literature on the subject. At the present time hardly a month passes without some phase of the problem being discussed in our journals.

PATHOLOGY

Numerous types of polyps are found in the colon and rectum. Each type has its origin in the different tissues of the bowel. Adenomas from epithelium, lipomas from fat cells, fibromas from submucosa, angiomas from blood vessels, myomas, lymphomas, etc. The mucous or adenomatous type are the most frequent and are the ones causing most concern because of their tendency to malignancy. To quote Rankin, "Of all the so-called precancerous lesions in the body, there is probably more definite proof that polyps of the colon are most likely to undergo malignant degenerative changes than lesions elsewhere." It is most significant that polyps and cancers occur in the same percentage of cases; that is, in the rectum and rectosigmoid area: 70 per cent for polyps and 71 per cent for cancer.

The tumors may vary in size from small raised elevations of the mucous membrane, a few millimeters in diameter, to pedunculated masses several centimeters in diameter. Ordinarily they are pedunculated but they may be sessile, or both varieties may be present in the same case. They will vary from a single tumor or several solitary polyps, limited to one or more segments of the bowel, to the case in which the mucous membrane of the entire colon is involved in the disease.

There is some difference among authorities as to classification and nomenclature due to incomplete knowledge of the exact etiology of the disease. Consequently we find many different terms in the literature. For practical clinical purposes the suggestion of Erdmann and Morris seems to be the simplest and covers the subject adequately, i.e., the familial, congenital, or disseminated type and the acquired, adult, or inflammatory type.

Familial, congenital, or disseminated type—The polyps are not present in susceptible persons at birth but make their appearance in childhood or near puberty. A tumor has been reported in a nine months old infant. There is overwhelming evidence to prove a definite familial relationship and also to substantiate the statement that all of these patients will develop cancer if they live long enough. It is concluded that the mucous membrane of the colon of these individuals has some inherent characteristic

*Associate Professor of Surgery, Department of Surgery, Georgetown University Medical Center, Washington, D. C.

C. EDWIN McNAMARA

which causes the formation of polyps.

Acquired, adult, or inflammatory type—Examinations of specimens of healing inflammatory lesions of the colon, and the finding of patches of normal mucous membrane pushed out from the wall of the bowel by the contracting scar tissue, are the bases for the inflammatory theory of etiology. As the tuft of mucous membrane is buffeted by the fecal stream it tends to become larger, pedunculated, and elongated. A large percentage of these lesions become true adenomas. Thus we see polyps resulting from ulcerative colitis, old strictures of the rectum, and hyperplastic tuberculosis, ulcerative colitis being the commonest etiologic factor. Although many polyps retain their adenomatous character throughout life, Fitzgibbon, Rankin and many other investigators have showed histopathologically definite progression of benign tumors to malignant degeneration.

SYMPTOMS

The symptoms of polyposis, of course, will depend on the amount of involvement of the colon, the amount of obstruction or ulceration present, and the amount of anemia or intoxication caused by the disease. Based on clinical observations the symptoms are as follows:

Pain—The pain is intermittent and cramplike in character. Practically all patients complain of some degree of abdominal discomfort.

Diarrhea—Loose stools with the passage of mucous is another constant finding.

Bleeding by bowel—The mucous diarrhea will become bloody as the disease progresses or as a result of trauma to the polyps by the fecal stream. The diarrhea and bleeding will alternate with constipation and succeeding attacks of bloody diarrhea.

Anemia and weakness—These findings will become manifest depending on the severity of the hemorrhage.

Anorexia, nausea, and vomiting—While not constant findings they will occur in conjunction with the other symptoms.

COMPLICATIONS

Anemia—As already pointed out, a secondary anemia will develop and sometimes very rapidly when the bleeding is severe.

Obstruction—Obstruction may occur in three ways: first, by occlusion of the bowel lumen by the direct growth of the polyps; second, by malignant degeneration of the polyps; and third, the tug of a polyp on the wall of the bowel sometimes will initiate an intussusception.

DIAGNOSIS

In all patients presenting any symptoms of large bowel pathology the following examinations are most essential and in this order:

Digital examination of the rectum—It is estimated that 60 per cent of large bowel lesions occur within reach of the examining finger. Another important factor is that diagnosis in this area cannot be made by the roentgenologist.

Proctoscopic examination—The proctoscope is a relatively simple instrument of great value, because it gives the examiner direct visual access to the rectum and rectosigmoid, an area in which 75 per cent of large bowel lesions occur. In addition, through the proctoscope, biopsies may and should be taken for microscopic study. Here again is an area where the x-ray is of little or no assistance.

X-ray examination—In addition to the usual barium enema x-ray the "combined double contrast" studies should be made. As described by

Fischer and modified by Weber, the procedure is conducted as follows: The patient is given the barium enema which is evacuated as quickly as possible. The colon is then insufflated with air until the cecum is filled and stereoscopic films are made. It should be stressed, and the roentgenologist would be the first to agree, that one negative x-ray study should not be considered final. If symptoms persist repeated examinations should be made.

TREATMENT

All authorities on the subject of polyposis of the colon are in complete agreement that the polyps should be eliminated. This may be accomplished first, by excision or second, by destruction in situ by electrofulguration, or by combining excision and fulguration. In all cases biopsy should be done to determine whether malignant degeneration has already started.

Solitary polyps in the rectum and rectosigmoid are reached easily through the proctoscope. Fulguration in these cases many times may be carried out as an office procedure.

Solitary polyps above the rectosigmoid may be removed by abdominal laparotomy and small incisions in the colon at the site of the lesions.

Multiple polyps limited to one segment of the bowel may be removed by resection of the involved segment and direct anastomosis.

It has been suggested that separate colostomies be done in the ascending, transverse, and descending colon, and scattered lesions be fulgurated through these openings, using the proctoscope. In this manner total colectomy would be avoided.

All authorities agree that cases with the familial type of polypoidosis should be treated by colectomy. The point of disagreement is whether or not the rectum and rectosigmoid should be preserved. The advantage of not removing them makes an ileosigmoidostomy possible, thus avoiding a permanent ileostomy with its attendant objectionable features. The point to be decided is whether or not the rectum and rectosigmoid present too much of a hazard as a site for recurrence and cancer. Even the advocates of ileosigmoidostomy recognize the danger and stress the importance of periodic follow-up examinations. The procedure in these cases is, first, fulguration of all lesions that can be reached through the proctoscope, and second, ileosigmoidostomy followed by colectomy down to the point of anastomosis.

The advocates of colectomy with removal of the rectum present an abundance of case reports of fatal recurrence to support their position. They feel that there is some factor inherent in the mucous membrane that makes a recurrence almost inevitable. They are attacking the problem of the permanent ileostomy in order to make it less annoying to the patient.

Ravitch with the anal-ileostomy avoids the abdominal opening. By his technic the rectum is removed but the sphincters are preserved and the ileum brought through them.

Ileostomies opening flush with the skin surface and discharging directly onto it create a terrific problem of management. They result in constant skin irritation, mental distress to the patient, and require much time and dressing for their care.

Cattell has proposed bringing the bowel out so that about one inch of ileum protrudes above the surface of the skin. This stump discharges into an appropriate bag and alleviates the skin distress.

Dragstedt modifies this principle by making the stump several centimeters in length and covering its sides with split thickness skin grafts. Many favorable reports are appearing in the literature of cases treated in this manner.

SUMMARY

A review of the current literature finds great emphasis that polyps of the large bowel are precancerous lesions.

The tumors should be removed by fulguration or excision.

In cases of the familial type, colectomy should be performed with removal of the rectum being considered. Recent reports of cases utilizing improved technics of ileostomy, indicate that removal of the rectum should be the operation of choice. That is, in the interest of avoiding recurrences and cancer.

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The Modern Treatment of Rheumatoid Arthritis

DARRELL C. CRAIN,[1] LAURENCE H. KYLE[2] AND MARTIN RUBIN[3]

GEORGETOWN UNIVERSITY MEDICAL CENTER, WASHINGTON, D. C.

Like most things modern the treatment of rheumatoid arthritis is at present in a state of turmoil. Indeed, it might be said that therapy in rheumatoid arthritis has reached the age of puberty—having passed through a rather unobtrusive infancy and childhood, it has suddenly entered into a stage of wild growth; and no one is quite sure what the future potentialities are for today's adolescent. One thing is sure, the adult stage of therapy, while closer today than yesterday, has not yet appeared. That physicians and patients alike should be looking for a magic bullet whose single administration will cure rheumatoid arthritis, even as Ehrlich 50 years ago sought a one package cure for syphilis is, of course, quite natural. And because of the stimulus given this hope by the discoveries of the past two years, it would seem appropriate at this time to examine the qualifications of certain of the compounds currently recommended as beneficial in the therapy of rheumatoid arthritis, and to attempt to draw some conclusions which might be of assistance in the treatment of this disease.

CORTISONE AND ACTH

It is fitting that these compounds be discussed first, since it was their application to rheumatoid arthritis that ushered in the "modern era." The epochal work of Hench and his co-workers[1, 2] has been summarized in detail in their most recent paper[3] and has been confirmed by numerous other investigators.[4-7]

At this hospital, cortisone or ACTH has been administered to 14 patients with rheumatoid arthritis with responses roughly similar to those previously reported by others. In brief, these may be summarized as follows: During the time that the drug is administered in adequate dosage, relief is afforded from the acute inflammatory signs and symptoms of the disease. Pain, swelling, and tenderness subside rather promptly, the muscle soreness and stiffness decrease, and greater mobility of the joints is attained. Concurrently there is general improvement manifested by increased appetite, increased sense of well being, and weight gain. The hemoglobin and red blood cell count increase and the sedimentation rate decreases. Fixed deformities, of course, remain unchanged, but contractures due to muscle spasm and fibrous thickening often show considerable improvement.

Maximum amelioration of signs and symptoms occurs within 2 to 10 days, although the drop in the sedimentation rate may be delayed longer, and persists as long as adequate dosage of the drug is continued (usually 100 mg. of cortisone, 40 mg. of ACTH, with somewhat larger doses being given on the first two or three days of therapy). No further benefit is apparent with larger dosage, while smaller doses usually are inadequate. Although this is the usual pattern, not all cases respond alike. Recent cases and those with the least amount of permanent damage receive the greatest benefit—often with dramatic results after the first injection. On the other hand, one of our long-standing cases showed very little objective or subjective change after 20 days of therapy.

[1]Instructor in Clinical Medicine;

[2]Assistant Professor of Medicine;

[3]Associate Professor of Clinical Pathology, all of Georgetown University Medical Center, Washington, D. C.

Following the withdrawal of the drug there is usually reversion to the pretreatment state within a variable time, 2 to 30 days in our cases. Some reported cases have taken longer to revert, while others note a "rebound phenomenon," in which signs and symptoms are more severe than before the use of the drug.

One of the chief problems in the administration of these drugs concerns the length of time they can and should be continued. Since the patient remains symptom-free while receiving them but relapses on withdrawal, one would be inclined to continue indefinitely. However, the continued administration of either cortisone or ACTH has been attended by certain undesired physiologic reactions. These include excessive fluid retention, rounding of the face, acne, hirsutism, impairment of carbohydrate metabolism, altered menses, nervousness, irritability, fatigue, delayed wound healing, and emotional changes ranging from euphoria to severe depression. Furthermore, to any discussion of these side effects must be added the fact that cortisone will depress the adrenal cortex, while ACTH will produce adrenal hyperplasia. Whether or not irreversible changes will take place in the gland following the administration of these drugs has not yet been ascertained.

As Hench has pointed out, the administration of cortisone and ACTH is still in the investigative stage where all physiologic reactions must be considered "effects." To the arthritic patients, the antirheumatic effects with improvement in joint symptoms, the antipyretic effect with lowering of fever, the nutritional effect with increased appetite and weight gain, the psychic effect with increased sense of well being, and the biochemical effect with increased hemoglobin and erythrocyte count, lowering of sedimentation rate, and restoration of normal serum protein ratio are all favorable and desirable "effects." Those other physiologic responses which occur, however, and which are not beneficial to the rheumatic patient have been designated "side effects." Nevertheless, the beneficial antirheumatic results are the first to appear while high dosage and long continued use of the drug are apparently the chief factors in the development of the unfavorable side actions—but certain individual variations in tolerance also exist, with men tolerating both hormones better than women.

To date, no optimal dosage or period of administration which will continue the beneficial yet forestall the detrimental actions has been determined. It may be better to give successive intermittent courses than to administer the drug continuously each day. After an initial 10 to 14-day period, it may be possible to give maintenance doses three times weekly. The addition of some agent to the solution to delay absorption so as to permit one injection per week, and the development of tablets for oral administration, are problems under investigation which will help to meet the problem of maintenance dosage. This, however, will not solve the question of side actions due to long continued administration. To date, there is no known solution.

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In the light of the foregoing facts, the question may well be raised as to the present place of cortisone or ACTH in the management of the patient with rheumatoid arthritis. From the purely scientific standpoint, the statement of Hench himself is undoubtedly correct, "as we have stated repeatedly, the use of these hormones should be considered an investigative procedure, not a treatment . . . It is hoped and believed that such studies will in time lead to an improved and practical method of treat-

ment. But this present study is to be regarded, not as a report on clinical therapy, but as an investigation in clinical physiology."

Had cortisone and ACTH remained in the research laboratories of hospitals and pharmaceutical houses and the reports concerning them been confined to medical journals, such a statement might have had practical value. However, cortisone has now been released to all hospitals on the approved list of the American Medical Association and all physicians in the United States have been advised of the fact. This has been supplemented in some instances by personal telephone calls from "detail men" to individual physicians, and the availability of the drug has been made known to the public at large by the lay press which has during the past year given prominent place to "the cortisone story." Thus, most patients with rheumatoid arthritis now know that cortisone is available—and most also believe that it will afford some relief from the suffering they have been experiencing. How, then, shall the physician answer the increasing queries he is receiving from his patients relative to the administration of the drug?

He might, in all honesty, simply state that the drug is still a research tool and that unless the patient is part of a rigidly controlled experiment, he does not recommend its use until more is known. This terse statement, however, will not dispose of the problem, since many persons who have been suffering for years are not so easily satisfied. In such instances, the physician must sit down with the patient and family, review the pros and cons of cortisone as a whole and as they may apply to the individual case under consideration, what it will do and what it will not do, the possible complications including the psychic depression secondary to a relapse after the cortisone remission, the cost of the drug, the length of time it is to be given, and what is to be done after the course of cortisone is completed. If, then, the patient is willing to assume his part of the responsibility, one would certainly feel justified in going ahead with its administration.

In view of the increased availability of cortisone and the increased number of patients to whom it will probably be administered, data should rapidly accumulate and at least some of the questions which now confront us should soon be settled. As a matter of fact, one may today wonder if cortisone will have any place in the ultimate therapy of rheumatoid arthritis. Its exact mode of action is not known and it is certainly not curative. Surely some day the true cause of this disease will be known and a specific form of therapy found.

OTHER STEROIDS

Hench's announcement of the antirheumatic effects of cortisone and ACTH immediately stimulated investigation of other steroids in an attempt to find one or more which might be more easily obtainable and nontoxic yet still have comparable physiologic effects. Indeed, some investigators had been working in this direction even before the Mayo Clinic reports. Although to date no other drug has been found with any significant action of this type, nevertheless the claims made for certain compounds both in the lay and medical press warrant their mention in this discussion.

Pregnenolone—Three separate investigators have recently reported enthusiastically on this product,[8-11] while a weekly picture magazine[12] has presented an ecstatic report extolling its therapeutic virtues, its presumed lack of toxicity, and its reasonable cost. A thorough review of the physiologic, pharmacologic, and endocrinologic aspects of pregnenolone has recently appeared.[13] In this review, it is stated that its use in rheumatoid arthritis was "suggested" as far back as 1946.

Despite these facts, the case for pregnenolone seems rather weak. Guest and his co-workers noted no improvement in 17 cases of rheumatoid arthritis and rheumatoid spondylitis.[14] When these facts were presented at the April, 1950, meeting of the New York Rheumatism Association, three out of four persons discussing the paper reported similar discouraging results. The fourth stated that although most patients did not respond, an occasional rheumatoid arthritic patient noted improvement under pregnenolone when other measures failed.

In the discussion following Ishmael's paper at the American Rheumatism Association meeting[11] additional investigators reported discouraging results. A recent editorial in the *Lancet*[15] also described the drug as without value. In the rheumatology clinic at Georgetown University Hospital, 6 patients were given oral pregnenolone in dosages of 300 mg. per day for periods varying from 14 to 60 days. Two cases were

given 500 mg. intramuscularly six days a week for four weeks. Only one of the 6 oral cases and neither of the 2 intramuscular ones showed significant improvement during the period of observation. Another case which did not respond to 14 days of pregnenolone did respond to cortisone and then relapsed when again started on pregnenolone.

The question therefore arises as to whether the improvement reported by Davison[6] as occurring in less than one week in 10 out of his 12 cases may not have been psychic. Furthermore, the treatment is not as inexpensive as people have been led to believe. As this article is written, the retail price is $60 for 100 tablets of 100 mg. each. This is enough for 33 days, since the recommended daily dose is 300 mg. Although this is considerably less than the cost of cortisone, the poor results generally reported would seem to make it too great to warrant recommending even a tentative trial.

Desoxycorticosterone actetate and vitamin C—The report of two European invertigators[16] that the administration of this combination produced relief of symptoms, often quite dramatically and within a matter of minutes, prompted many physicians to test its therapeutic effectiveness in rheumatoid arthritis. Although a few who have reported on this approach have been enthusiastic,[17-19] with one[17] going so far as to state that it is possible that this method "holds out the most immediate promise of relief to sufferers from this disease," nevertheless the overwhelming opinion of critical investigators is that the combination of desoxycorticosterone and vitamin C is of little or no use as a therapeutic agent in rheumatoid arthritis.[20-26] Twelve members of England's Empire Rheumatism Council reported[24] that they had "unanimously found this treatment of no significant value in rheumatoid arthritis." Of their combined 172 cases, only 3 showed objective improvement and only 11 felt any subjective response. Three out of 14 cases studied by Kling[26] had rather serious toxic reactions.

Testosterone, progesterone and others—Ishmael's[10, 11] enthusiasm for testosterone does not seem to be shared by others,[14, 15, 27] while the previously reported thorough studies of progesterone here at Georgetown[28] and a clinical test in England[29] were entirely negative and failed to confirm Reich's rather optimistic report.[30] Screening studies were done here at Georgetown on testosterone, dihydrotestosterone, 21 acetoxy pregnenolone, and 17 hydroxy-delta 1 pregnenedione. No therapeutic response was noted to any.

SUMMARY OF STEROID THERAPY

An appraisal of studies at Georgetown University Hospital relative to the effects of cortisone, ACTH, pregnenolone, progesterone, testosterone, dihydrotestosterone, 21 acetoxy pregnenolone, and 17 hydroxy-delta 1 pregnenedione, and a careful review of the literature to date makes the authors agree with the editors of the *Lancet* when they state that "the position, therefore, still is that no substances, except cortisone and ACTH, can yet be held to have substantiated their position in the endocrine treatment of rheumatoid arthritis." Certainly, further critical objective evaluation of all steroid therapy is needed.

CALCIUM SUCCINATE COMPOUNDS

Although very little has appeared in the medical literature either for or against the combination of salicylates and calcium succinate, nevertheless the tremendous amount of advertising of the proprietary products Imdrin and Dolcin warrants mention of them in this review. Dolcin is a combination of calcium succinate and aspirin alone, while Imdrin contains calcium succinate with smaller doses of aspirin, plus phenacetin and caffeine. The advertising material of each claims that the addition of calcium succinate advances the antirheumatic effect of the medication.

Two separate clinical evaluations of Dolcin have been made, one at Georgetown Hospital[31] and one at Presbyterian Hospital in Newark, New Jersey.[32] The results in both were similar: this product has no value over aspirin alone in the treatment of rheumatoid or osteoarthritis. Because of its false advertising Dolcin has recently been the subject of action by the Food and Drug Administration and has revised its publicly stated claims so as to omit the previous obnoxious statements. It is hoped that this information will be disseminated as widely as possible, so that the public may be protected from paying $3 a bottle for a drug whose actual value is 50 cents worth of aspirin.

In the light of the foregoing discussion, one may well ask, "what is the 'modern' treatment of rheumatoid arthritis, and how does it

differ from previous treatment?" The immediate answer to this question would be that nothing has appeared in the past two years to alter the basic concepts of treatment as previously accepted and recorded in the "Primer" prepared by the A.R.A. in 1949.[33] The "measures of proved value" including adequate local, general, and mental rest, proper exercises (also local and general), proper nutrition without recourse to fad diets, the correction of body defects, including transfusions for anemia and removal of definitely infected foci, aspirin to relieve pain, and properly administered physical therapy must still be regarded as the sine qua non of treatment in rheumatoid arthritis. In other words, the restoration of the organism to its optimal physiologic function is still the goal to be sought. In many cases this will be all that is necessary; in no case should it be neglected in the hope of finding a short cut type of cure.

If, however, something further should be indicated by the progress of the disease despite these general measures, one is justified in using those "measures on which there is fairly uniform agreement" including gold, which still has its place high on the list of useful modalities. Forestier, who is generally credited with having first used gold in the treatment of rheumatoid arthritis, has suggested[34] that a combination of gold and cortisone may be more effective than either alone. This is an interesting possibility, and would seem to fit into the picture as useful in terminating acute attacks in early cases, or as a means of giving relief from some of the severe suffering in later cases.

SUMMARY

A brief resume of the hormones currently recommended as of value in treating rheumatoid arthritis indicates that only cortisone and ACTH have antirheumatic properties. Compounds of calcium succinate and aspirin have no value over aspirin alone. To date, no short cut has been found in the treatment of rheumatoid arthritis, and the therapeutic regimen must be based, as before, on a sound physiologic approach.

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Hemophilia Simulating Acute Surgical Abdomen

MARGARET SHELTON[1] AND HUGH H. HUSSEY[2]

GEORGETOWN UNIVERSITY MEDICAL CENTER, WASHINGTON, D. C.

HEMOPHILIA is an hereditary disease characterized by an abnormally long coagulation time. Although considered a rare disease, it is the most common of the congenital hemorrhagic diseases,[1] and the fact that the hemophiliac patient requires numerous hospital admissions during his lifetime makes hemophilia a fairly common disease in general hospital practice. This is shown in the two cases reported below. One patient had had approximately 75 previous admissions for bleeding episodes and the other had had 47 previous admissions.

Although hemorrhages of hemophilia may occur spontaneously, usually they follow trauma. The trauma may be so slight that the patient scarcely remembers it at the time his symptoms appear, and the extent of the hemorrhage may be far greater than would be expected with the amount of trauma. Characteristically, the bleeding of hemophilia is into the deep structures: muscles, bones, joints. This may help distinguish hemophilia from other hemorrhagic diseases, such as thrombopenic purpura, in which the bleeding is often an oozing from the mucous membranes.

The hemorrhages of hemophilia may occur in any location, and to distinguish the symptoms of hemorrhage from those of other diseases, which also occur in hemophiliacs in the same ratio as in the general population, often requires astute clinical judgment. The most frequent site of bleeding in the adult hemophiliac is into the joints, and chronic hemophiliac joints have often been described in the literature. Pseudotumors of bone, especially of the hands and feet, are not uncommon. Epistaxis, laryngeal obstruction due to hematoma, hematuria, pleural and parenchymal lesions of the lung, and numerous neurologic lesions have also been described.[2]

Intra-abdominal hemorrhage is one of the most serious forms of bleeding because of the high mortality which accompanies exploration in the hemophiliac who has not been prepared for surgery by adequate antihemophilia therapy, and also because of the complication of hemorrhage at the site of other acute disease, such as cholecystitis. The differential diagnosis is difficult. Lower abdominal pain is said to be the most frequent of all abdominal emergencies in hemophilia.

The most common sites of hemorrhages are in the colon wall or the mesocolon, where the signs are those of partial obstruction, and into the iliopsoas muscle, where the signs resemble those of acute appendicitis. The pain is usually in the right lower quadrant with hemorrhage into the iliopsoas. Although the pain seldom starts in the epigastrium, it may begin insidiously and become much more severe in twenty-four hours, with exquisite tenderness and rebound tenderness over McBurney's point. Rectal pain

[1]Assistant Resident in Medicine, Gallinger Municipal Hospital, Washington, D. C.

[2]Associate Professor of Medicine, Georgetown University Medical School.

From the Georgetown Medical Service, Gallinger Municipal Hospital, and the Department of Medicine, Georgetown University School of Medicine.

is usually more severe on the right side. Vomiting and cramping abdominal pain may occur. Low grade fever and a moderate leukocytosis are usually present. In one series of 40 hemophiliac patients followed for several years, 15 had had at least one episode of lower abdominal pain.[2]

THE two cases reported here exemplify the difficulties which may be encountered in management of lower abdominal pain in the hemophiliac patient.

Case 1—A 15-year-old Negro male, known to have hemophilia, was admitted to the medical service September 12, 1948, complaining of periumbilical pain and constipation. Seven days before admission, while sitting in a movie about 2 hours after eating, the patient noted progressively severe periumbilical pain. The pain became so severe that he had to leave the movie about 30 minutes later. At that time he vomited a clear, bitter, yellow liquid. At first he vomited only after ingestion of food or water, but for 3 days before admission he vomited "almost constantly." His stools were tarry 6 days before admission, and for 5 days before admission he had no stools, although he passed flatus daily. The pain had persisted, located periumbilically without radiation and unrelieved by change in position.

He had been known to have hemophilia since the age of 3 years and had had 47 previous hospitalizations for bleeding episodes. All of the episodes were apparently spontaneous. The left hip, knees, and ankles were the most frequent sites of involvement. Each of the episodes had been controlled with transfusions of whole blood.

The patient was the youngest of three children, all males. Both brothers were proved hemophiliacs. No history of bleeding tendency in grandparents, uncles, or nephews was obtained.

On examination the patient looked acutely ill. He was lying flat with knees flexed, groaning, and clutching his abdomen. Pulse was 100; temperature 98.6; blood pressure 120/60. There was evidence of severe dehydration. The abdomen was distended and firm. There was pain, splinting upon light palpation and rebound tenderness universally. No peristalsis was heard. The rectum was filled with tarry stool and rectal examination was painful, more so on the right than on the left side. There was slight limitation of motion of the left hip and the left leg was shorter than the right.

Laboratory data on admission were as follows: hematocrit 37; hemoglobin 88 per cent; leukocyte count 9,200 with polys 68 per cent, bands 3 per cent, lymphs 27 per cent, monos 2 per cent; erythrocyte count 4,900,000; corrected sedimentation rate 2 mm.; icterus index 5; prothrombin time 72 per cent of normal; Rumpel-Leedes test negative; bleeding time 3 minutes; clotting time 88 minutes; clot retraction time 60 minutes; platelet count 150,000; stools, guaiac positive.

The patient was seen by a surgical consultant who concurred in the diagnosis of intra-abdominal hemorrhage, both intra- and extra-luminal. He was given analgesics, a transfusion of 500 cc. of whole blood, infusions to correct dehydration, and Wangensteen suction. The suctioned material, at first tarry and guaiac positive, cleared to a yellowish-green, guaiac negative fluid in 6 hours. Normal peristalsis was heard 18 hours after admission, and a tarry stool passed 24 hours after admission. Suction was discontinued at that time.

On the morning of the second hospital day, clotting time was 60 minutes. He was given 200 mgm. of antihemophilia globulin in normal saline, and 4 hours later the clotting time was 14 minutes. A transfusion of 500 cc. whole blood, 75 mg. of vitamin K, and 200 mg. of antihemophilia globulin were given, and 4 hours later the clotting time was 8 minutes. On the third hospital day the patient was given fluid by mouth, and thereafter the diet was gradually enlarged. He was discharged on the eighth hospital day at which time his clotting time was 40 minutes.

Case 2—A 32-year-old white male, known to have hemophilia, was admitted to the medical service October 17, 1948. Three days before admission the patient became aware of an aching pain in the lower part of the abdomen. The pain was more severe when he moved his bowels, although the stool was of normal color and consistency. Two days before admission, the pain was more severe in the left lower quadrant, but on the day he sought admission the pain became sharp, constant, and localized in the right lower quadrant. There was no nausea, vomiting, or disturbance of bowel function. Pain was slightly relieved by flexion of the knees. He had noted slight right lower abdominal tenderness. The patient described 3 previous bouts of right lower abdominal pain occurring during the preceding 10 years, but it had never been so severe and had always been relieved by bowel movement.

Hemophilia had been diagnosed at the age of 1 year and the patient had had 75 previous hospitalizations for bleeding episodes. He had lost vision in the left eye due to intra-orbital hemorrhage 9 years previously. One episode of tarry stools was described 11 years before this admission. He had had no other gastrointestinal difficulties until the present illness. His hemorrhages were previously treated with transfusions of whole blood.

Two brothers had died in childhood as a result of massive hemorrhage due to hemophilia; one at 3 years, one at 5 years of age. The son of his sister was a known hemophiliac. The bleeding tendency could not be traced beyond this generation.

The patient looked acutely ill and in severe pain. Pulse 90; temperature 98.6° F.; blood pressure 138/88. The left eye appeared sunken, with only a narrow strip of cornea visible. The abdomen was flat and rigid. Tenderness and rebound tenderness were elicited in the right lower quadrant. Peristalsis was hypoactive. Rectal examination showed bleeding external hemorrhoids. Both knees were larger than normal, and flexion was limited to 90 degrees.

Laboratory work on admission was as follows: hematocrit 42; hemoglobin 13 gm.; leukocyte count 12,500, with polys 73 per cent, bands 5 per cent, lymphs 22 per cent; corrected sedimentation rate 13 mm.; platelet count 101,280; icterus index 7.5; venous clotting time 70 minutes; bleeding time 2 minutes.

Fourteen hours after admission the patient developed exquisite, constant, right lower quadrant pain. A sur-

gical consultant concurred in the diagnosis of acute appendicitis and abdominal exploration was advised. The patient was given 600 mg. of antihemophilia globulin and a transfusion of 1,000 cc. of whole blood. Clotting time immediately before operation was 18 minutes.

Under general anesthesia, the abdomen was opened through a right McBurney incision. Upon opening the peritoneum, there was a gush of freely flowing, old blood. Approximately 750 cc. of blood was removed from the abdominal cavity by suction. None was thought to be of recent origin. Manual exploration through the incision revealed what was thought to be a massive hematoma of the mesentery. Further exploration was considered ill-advised, and the abdomen was closed. Immediate postoperative condition was fair.

During the first three postoperative days the clotting time was maintained as close to normal as possible with antihemophilia globulin and fresh plasma. Clotting times on these days were 13 minutes, 15 minutes, and 14 minutes. The postoperative course was uneventful. Further questioning revealed that 10 days before admission he had dropped a 2,000-year-old funeral urn in the museum where he was employed. In order to prevent breakage he had let it fall against his abdomen. This was the only trauma he could recall. He was discharged on the ninth hospital day at which time his clotting time was 17 minutes.

DISCUSSION

At the time of their admissions both of these patients were known to have hemophilia. The main problem was whether their symptoms were due to a bleeding episode or to acute appendicitis. In the first case, intra- and extraluminal hemorrhage seemed most probable because of the tarry stools and coffee ground vomitus and signs of generalized peritoneal irritation. The treatment therefore was directed to correcting the coagulation defect. The rapid regression of symptoms substantiated the impression that intra-abdominal hemorrhage was the sole cause.

In the latter case, within the first 14 hours after admission, the patient's clinical condition progressed unfavorably to such extent that surgical intervention appeared imperative. He was rapidly prepared for operation with antihemophilia globulin and the abdomen was explored as soon as the coagulation time approached normal. The diagnosis of intra-abdominal hemorrhage was established at operation, although the signs and symptoms were clinically those of acute appendicitis. The confusion of appendicitis and bleeding in hemophilia is so frequently encountered that Quick has stated, "It should be remembered that any sudden symptom appearing in a hemophiliac should be considered arising from hemorrhage until proven otherwise."[1]

Quick has described the process of coagulation as autocatalytic, originating in the platelets, which upon disintegration liberate an enzyme which acts on the precursor of thromboplastin, thromboplastinogen, converting it to active form. Thromboplastin then reacts to form thrombin which in turn combines with fibrinogen to produce fibrin. Thrombin also causes labilization of platelets so that more enzyme is available.

EXPERIMENTALLY it has been established that the platelets of hemophilia are fully active quantitatively and qualitatively when the environment, the plasma, is normal. The defect in coagulation in hemophilia is therefore not in the platelets, but rather in the plasma.[1] Competent investigators have shown that in hemophilia there is no deficiency of calcium ion, of prothrombin, nor fibrinogen.[3] The defect, therefore, is thought to be a deficiency of thromboplastinogen.

Certain globulin fractions of normal plasma, obtained by acid precipitation or by dialysis against distilled water or tap water, possess the property of correcting the defect of coagulation in hemophilia. Similar preparations from hemophiliac blood do not correct the coagulation defect. Cohn and his co-workers, using large amounts of fractioned human plasma, have found the antihemophilia activity to be concentrated maximally in Fraction I, Subfraction II of Fraction III, and in small amount in Fraction IV.[3]

The classical criteria for the diagnosis of hemophilia are a familial history of bleeding tendency, a personal history of bleeding, and a demonstrable increase in venous clotting time. To these might be added the return of the coagulation time toward normal after the administration of antihemophilia globulin. The diagnosis is usually established during childhood. Patients in the age group of 3 years to 10 years are most frequently hospitalized for acute hemorrhage, possibly because of physical hyperactivity. Approximately 70 per cent of the patients give a familial history of a bleeding tendency.[4]

Although the coagulation time of venous blood which is free of tissue juices is characteristically prolonged, mild hemophiliacs with nor-

mal coagulation times have been reported. The clot retraction time, Rumpel-Leedes test, bleeding time, platelet count, and prothrombin time are normal.[5] However, it has been shown in hemophilia that the clotting time of recalcified plasma obtained by fast centrifugation is longer than the clotting time of recalcified plasma obtained by slow centrifugation, whereas the speed of centrifugation of the clotted blood has little effect on the clotting time of normal recalcified plasma.

The prothrombin consumption test (prothrombin time done one hour after a clot has appeared in unoxalated blood using fresh oxalated plasma treated with tricalcium phosphate as a source of fibrinogen) is usually 9 to 12 seconds in hemophilia, whereas the normal range is 16 to 30 seconds.[1] These tests, while unnecessary in the classical case, have been used to establish the diagnosis when the cause of the bleeding tendency is obscure.

THE treatment may be divided into (1) local and general measures during an acute episode of bleeding and (2) attempts at long range therapy. The local measures used successfully in controlling hemorrhage following trauma, such as laceration and tooth extraction, are nonspecific. They include cold applied to the area, pressure bandages, fibrin foam, thrombin, electrocautery, gelatin, epinephrine, muscle or placental extracts, and application of globulin of bovine, rabbit, swine, or human source.[6] If the hemorrhage is not controlled by simple and available local measures, or if there is internal bleeding, general therapy should be instituted.

As early as 1916, transfusions of whole blood were found to correct the coagulation defect. This is still the most generally available therapeutic method and is indicated in any instance when anemia is present. Usually a single venoclysis of 500 cc. of whole blood will control acute hemorrhage.[6] If it is available, and there is no anemia to be corrected, 200 mg. of antihemophilia globulin Fraction I, dissolved in 5 to 10 cc. of isotonic saline is as effective as a transfusion of whole blood.[3] Freshly processed, frozen normal human plasma may be administered with the same excellent therapeutic results. Volume for volume, it is twice as effective as whole blood. Alexander has reported that the effect of plasma, blood or globulin may last from 2 to 6 days.[7] During an acute hemorrhagic episode or in preparation of the hemophiliac for surgery and during the immediate postoperative days, one of these agents is administered until the clotting time approaches normal. Treatment is continued until the immediate crisis is past.

No satisfactory method of maintaining the clotting time within or near normal over long periods of time has yet been established. Refractoriness to blood, antihemophilia globulin, and plasma have been reported.[1] Therefore these measures are usually employed only during the time of an acute hemorrhagic episode or when surgery is contemplated.

SUMMARY

1. Two cases have been reported in which hemophilia was responsible for abdominal symptoms suggesting a surgical emergency.

2. Criteria for the diagnosis of hemophilia include the family history of bleeding tendency, a personal history of bleeding, increase in clotting time of venous blood, and return of the clotting time toward normal after administration of antihemophilia globulin.

3. Besides local measures, treatment of an episode of acute hemorrhage in a hemophiliac may include transfusion of whole blood or plasma or administration of antihemophilia globulin.

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GENERAL PRACTICE *Review*

To provide the general practitioner, as well as the specialist with concise, readily available information on the latest, proved methods of treatment of conditions commonly encountered in an average practice, POSTGRADUATE MEDICINE *offers this department to its readers. It is not, of course, intended to present these discussions as the only acceptable therapeutic procedures to be used, but rather to offer simple regimens and recommendations based on the extensive experience of the physicians who prepared these summaries.*

Management of Prostatitis

RUSSELL D. HERROLD

UNIVERSITY OF ILLINOIS COLLEGE OF MEDICINE, CHICAGO

THE management of prostatitis is by far the most common problem confronting the urologist in his office practice. While in many respects the massage of such an area of infection would not seem to be a logical procedure, it is still recommended for lack of a better method of treatment. Certainly, establishment of drainage relieves many patients of their objective and subjective symptoms and in some instances is followed by cure as measured by a return of the prostatic secretion to normal.

A combination of increased drainage and other adjuvant measures should be continually investigated, however, in the hope of improving the results. The various antibacterial agents should receive careful evaluation as an added means of eradication of infection.

While the flora of chronic uncomplicated nonspecific prostatitis in many instances are susceptible in vitro to penicillin within the therapeutic range, successful eradication does not always follow the administration of this drug. In a series[1] of 63 infections of this type, it was found that 1/10 unit of penicillin prevented growth in vitro in 24, with partial inhibition in 23, and no effect in 16. Yet administration of penicillin to the group with most susceptible bacteria resulted in cure in only one-fourth of the patients, with some improvement in a like number.

It is probable that the nature of the infection prevents suitable dissemination into all the areas of infection within the gland so that after discontinuance of the antibiotic a general reinfection occurs. As a rule, the exudate obtained after prostatic massage will not yield a growth of bacteria during the administration of penicillin to patients with bacteria previously proved susceptible in vitro to the drug.

The proper selection of patients for a particular type of treatment is of considerable importance. There should be a careful clinical and laboratory appraisal of the infection in order to determine if limited to the lower urinary tract and if so, uncomplicated by associated disease. The type of offending bacteria should be recognized at least to the extent of whether they are Gram-positive or negative organisms or mixed. Cultures should be utilized when available and sensitivity tests are desirable if antibiotics are to be administered. Obviously, in general practice, cultures and sensitivity tests are not always practicable, but for investigational purposes they are a necessity.

The presence of infection in the bladder and upper urinary tract produces a constant reinfection of the prostate and lower urinary tract so that successful management requires eradication of infection from above. This usually entails correction, often by surgical measures, of the underlying cause of such chronic infection. Here the offending bacteria are much more likely to fall in the groups of various Gram-negative bacilli while uncomplicated prostatitis has as its flora Gram-positive bacteria

such as staphylococci, streptococci, and diphtheroids.

The role of foci of infection outside the urinary tract would seem to continue of sufficient importance that a search should be made and eradication carried out when so indicated.

A standard history should include leads as to the most probable type of infection to serve as a guide for the type of urologic examination. The present day history should include additional information. Since many of the patients have had previous treatment without success, knowledge of such therapy serves to some extent as a therapeutic test. Also patients should be questioned carefully as regards sensitivity reactions from previous administration of any of the common antibacterial agents.

The clinical and laboratory appraisal of infections is an important procedure. The patient with prostatitis may have an associated urethral discharge. This should be examined first by a Gram stain to rule out gonococcal infection, to determine the type of other bacteria or the total absence of bacteria, as occurs in the so-called abacterial pyuria. A wet preparation should also be examined to rule out the presence of trichomonads.

A great deal of information can be obtained by the simple 3 glass test, the first two before prostatic massage and the third afterwards, since occasionally insufficient prostatic secretion is obtained, and the washings in the 3 glass test are needed to make the diagnosis. In uncomplicated nonspecific prostatitis the first glass is usually clear with a few shreds and/or flocculi and the second glass is entirely clear.

In making a digital examination of the prostate, common conditions encountered for differentiation are hyperplasia, calculus, carcinoma, and tuberculosis. The latter, however, involves seminal vesicles more commonly. The prostatic secretion should be collected, preferably in a container or watchglass, and a drop which represents a fraction of the whole examined microscopically, first under low power and second under high power, noting the presence of pus cells and other abnormal constituents.

If a Gram stain is desirable, it is best to dilute the secretion with about 3 parts of water, since this assures more clearcut distribution and a more satisfactory Gram stain. If insufficient secretion is obtained, however, the urine voided after prostatic massage should be centrifuged and the sediment examined. Frequently on the first examination there may be insufficient pus cells to establish a diagnosis, whereas after a second or third massage there will be a definite increase in the pus cell content. It has not been my experience that there is an increase in pus cells after repeated massage in patients with normal prostates.

Management of nonspecific uncomplicated prostatitis limited to the lower urinary tract consists chiefly of regular prostatic massage twice a week for about six weeks, and then once weekly for a like period. If the prostatic secretion is not normal following this treatment there should be a rest period of several weeks during which time there may be a gradual return to normal. Certain adjuvant measures may be used in connection with the routine prostatic massage such as the administration of one of the sulfonamides, although in my experience these drugs have not been highly beneficial. As stated previously, penicillin in selected instances has been of some value. The use of certain antibiotics or a combination of antibiotics would seem worthy of a trial.

Nonspecific prostatitis may be complicated by a urethritis which is usually influenced favorably by administration of one of the sulfonamides or antibacterial agents. Stricture may be associated with infections of the prostate and if present should receive appropriate treatment.

Epididymitis is generally secondary to infection of the prostate and in my experience responds better as a rule to administration of sulfonamides than it does to penicillin. However, if this complication is suspected to be due to one of the coccal organisms, penicillin may be administered in addition to the sulfonamides. If due to one of the Gram-negative bacilli, one of the sulfonamides is administered first and if there is not a prompt favorable response, streptomycin or dihydrostreptomycin is administered in a daily dosage of ¾ gm. as an additional therapeutic measure. With such a dosage for a period of six days we have been able to cure many chronic uncomplicated infections of the bladder and upper urinary tract due to coliform bacilli and it would seem about as effective as the more frequent administration given hospitalized patients.

Although a certain percentage of patients with prostatitis have an associated seminal vesiculitis, this condition is not as frequent as before the successful methods of therapy for gonococcal infections became available.

Gonococcal prostatitis is rare in patients who submit to treatment promptly after the onset of infection. Neglected infections, however, are likely to extend posteriorly and here, while the gonococci can be easily eradicated, the associated secondary bacteria remain, producing the so-called postgonococcal prostatitis which may be quite resistant to penicillin or other antibacterial agents.

Abacterial pyuria is quite rarely encountered and generally involves the lower urinary tract in persons between 20 and 40 years of age. If not

cured promptly, there may be symptoms of involvement of the upper urinary tract. Sulfonamides, penicillin, and streptomycin are of no value. The response has been quite satisfactory to neoarsphenamine or mepharsen. Abacterial pyuria is assumedly a virus disease. We have seen 2 patients recently who responded dramatically to administration of chloromycetin with complete relief of subjective and objective symptoms in forty-eight hours. It is well to continue administration of chloromycetin for six days to avoid the possibility of relapse.

Trichomonas infestation in the male is rare as compared to that in the female and most generally occurs in men whose wives are so infected. If limited to the urethra a favorable response usually follows the instillation of acriflavin 1:4,000 daily. Infection in the prostate may be eliminated by prostatic massage alone. Carbarsone has been suggested as an added therapeutic measure in a dosage of 0.25 gm. three times a day.

Prostatitis secondary to infection of the bladder and upper urinary tract is more often due to one of the various Gram-negative bacilli or to mixed infection. It has been my experience that eradication of the Gram-negative bacilli from the bladder and upper urinary tract is soon followed by their absence in the prostatic secretion unless this gland has such complications as calculi, dilated prostatic ducts, or other causes of faulty drainage. It is obvious that the primary cause of such chronic infection in the bladder and upper urinary tract must be corrected before this type of prostatitis can be cured.

Acute prostatitis with infection limited to the lower urinary tract is comparatively rare and responds promptly to administration of one of the antibacterial agents. Prostatic abscess is even more rare but suitable drainage is required just as before the advent of effective chemotherapy.

Tests of sensitivity to the various antibiotics can be made by the simple procedure[2] of inoculating the prostatic secretion or the urine directly onto solid culture medium containing concentrations of the antibiotics comparable to that which may be obtained in the serum or tissues through their administration. This method gives not only the number of colonies of the various organisms but also their relative sensitivity to the different antibiotics. If a single dilution is used, we have found 1/5 of a unit of penicillin and 20 units of streptomycin to be the optimum concentration in the test medium.

Combined therapeutic measures are advisable in the presence of mixed infections. Penicillin may be combined with one of the sulfonamides or with streptomycin. Such combinations may also be used when there is a single offending organism, for their additive effect and possibly for a synergistic action, particularly for proved resistant bacteria. A sulfonamide under investigation known as Gantrisin (NU-445) is more soluble than prior sulfonamides and produces comparatively few side reactions even in dosages of 6 gm. daily. It would seem to be ideal for combination with the antibiotics.

There have been insufficient observations for the evaluation of the two newer antibiotics, aureomycin and chloromycetin, in chronic prostatitis. The bacterial flora of chronic prostatitis is within the range of therapeutic efficacy in most instances. These agents may prove to be of some value, and since they can be given orally, their administration will be practicable in office practice. We have administered these drugs to a few patients with chronic prostatitis but their exact indications have not as yet been determined.

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Treatment of the Common Cold

NOAH D. FABRICANT

UNIVERSITY OF ILLINOIS COLLEGE OF MEDICINE, CHICAGO

Despite a burst of advertising pyrotechnics seldom seen in the field of medicine, the American medical profession is beginning to realize that the common cold cannot be "stopped" by extravagant and irresponsible claims in behalf of antihistaminic drugs. The facts of the matter are that no substance or combination of substances currently available can be relied on to prevent or cure the common cold. Controlled studies of products which now appear on the market reveal that

many of them make claims regarding the treatment or prevention of the common cold which are not justified by valid evidence. Advertisements in the press and over the air exaggerate the effects which the medicaments will have on symptoms. Consequently, the general public continues to spend huge sums of money unnecessarily not only on the "miracle-drugs" but also on other illogical remedies, such as rubbing remedies, salves, and ointments. It will continue to do so until it is educated to the foolishness of such practice.

NOSE DROPS AND INHALANTS

A number of simple agents and measures exist which patients can be taught to employ for temporary relief and from which little harm will result. In this connection, the use of nose drops and inhalants ranks high among measures taken by the public to relieve nasal distress. Nasal vasoconstrictors afford symptomatic relief for varying periods of time but are not curative. Liquid nasal medicaments which function on a rational, physiologic basis are compatible with ciliary activity, do not vary greatly in their *p*H (5.5 to 6.5) from that of normal nasal secretions, are isotonic, and are noninjurious and nontoxic. Prolonged and excessive use of nose drops and volatile inhalers occasionally results in secondary rebound congestion of the nasal mucous membranes. Prolonged administration of silver salts can produce argyrosis, while the continued employment of nasal preparations containing mineral oil sometimes leads to the development of lipid pneumonia.

GARGLES

Although popular with the public and with some physicians, gargling has little therapeutic utility. Ordinarily, gargles do not provide medication behind the anterior pillars of the fauces. It has been found that gargled materials will not pass beyond the third molar tooth, thereby reaching neither the tonsillar nor pharyngeal areas, because the act of gargling produces a restrictive influence. In most cases of acute, uncomplicated pharyngitis, a reasonable amount of relief may be obtained by irrigating the throat with hot, isotonic solution of sodium chloride by means of syringes or modifications of a douching apparatus.

SALICYLATES AND COUGH MIXTURES

Acetylsalicylic acid does not have any influence on the infectious process of the common cold. Nevertheless, symptomatic relief of headache, fever, and muscle pain is of value as long as the drug does not disguise the need for more vigorous treatment. Occasionally, a false sense of improvement occurs, stimulating the patient to premature activity. Numerous cough mixtures to which laymen often resort without the advice of a physician are of dubious value. Expectorants or respiratory sedatives are best prescribed by physicians, since cough mixtures should be governed by the type of cough and the age of the patient.

DIET

From time to time claims are advanced advocating a special diet either for the prevention or cure of colds. The dietary measures most frequently recommended for the prevention of colds include a high protein diet, a diet low in carbohydrates, and large quantities of citrus foods, presumably to establish "alkalinization." None of these theories is supported by carefully controlled studies. The supplying of extra vitamins and other food elements to the individual who does not show signs of deficiency disease does not protect him against colds. So widespread is the belief of the American public that the use of sodium bicarbonate or other antacids is a preventive in the treatment of the common cold that it may really be called a part of American folklore. It has been demonstrated conclusively that the results obtained by "alkalinization" are of little or no value. Procedures which have as their objective the conditioning of the body to sudden changes in external temperature of the skin, such as cold and hot shower baths, do not lower the incidence of the common cold. The scientific evidence against the value of oral cold vaccines is overwhelming.

SYMPTOMATIC RELIEF

Although frequently ignored because of the widespread belief that nothing much can be done about the common cold ("there is only one way to treat it—with contempt" is a practice as current today as it was in ancient Rome), the treatment of the common cold consists mainly in the relief of symptoms as they arise. Treatment should never be standardized but should be suited to the needs of each patient. During the earliest stages of the common cold the prime objective is to supply moisture by means of steam inhalations to the stricken upper respiratory passages.

Alcohol has been utilized for generations to abort impending colds or to treat them. In reasonable therapeutic doses it causes peripheral vasodilatation and re-establishes circulation in chilled cutaneous and mucosal surfaces. Little attention need be paid to fluids in the average uncomplicated cold; it is probably best to let thirst to a great extent determine the fluid intake. Cathartics and laxatives, long employed as home remedies for colds, do not have particular value; their excessive use may lead to dehydration.

Rest in bed, especially if fever is present, diminishes the severity of the common cold, limits its spread to others, and reduces the frequency of complications. It has stood the rigid test of time as a most sane and effective measure.

EDITORIALS

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Editor-in-chief: CHARLES W. MAYO, M.D.
Contributing Editor and Editorial Writer: MORRIS FISHBEIN, M.D.
Assistant Editor: SYLVIA COVET

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"WHAT IS THE PRACTICE OF MEDICINE?"

For some years a difficult situation has existed in medical practice, as yet unresolved, having to do with the work of the anesthetist, the pathologist and the roentgenologist in hospitals and the marketing of the services of these specialists by the hospital acting as a corporation. Several distinguished committees of the American Medical Association have conferred on this subject from time to time with committees and boards of the American Hospital Association, and the situation has been resolved by mutual agreement. The primary feature is the placing of the responsibility for methods of practice on the individual hospital and the medical society in the county in which the hospital is situated.

Recently the American Hospital Association indicated its belief that the practice of radiology, pathology, and anesthesiology in hospitals is a portion of hospital care. According to an editorial in the *Modern Hospital* the American Hospital Association said, "that the economics of such hospital departments must be worked out between the hospitals and physicians concerned and cannot be dictated by national organizations."

A long editorial in the *Modern Hospital* entitled "What Is the Practice of Medicine?" is a beautiful example of the kind of oversimplification in which laymen frequently indulge when discussing medical problems. It is easy to say that a man who tells his neighbor to take some aspirin is not practicing medicine and to argue from this that a nurse who administers an anesthetic to a hospital patient is not practicing medicine. It is easy to say that the manner of collecting fees has nothing to do with the practice of medicine. Out of this confusion the writer of the editorial comes to the conclusion which he places in italics that "the practice of medicine is whatever is done professionally by the physician." In other words, if the doctor takes care of the patient, the doctor is practicing medicine; if anyone else is caring for a patient that person is not practicing medicine. What then is the value of laws regulating the practice of medicine? What protection has the public against the practice of highly technical procedures by incompetent and untrained personnel?

The editorial in *Modern Hospital* completely avoids the chief issue involved in the discussion of this problem. The issue concerned has nothing to do with the fee or how the fee is collected. The issue goes

clearly to the point that the hospital is a corporation, that the physician is an individual practicing a profession, and that marketing professional services by corporations which develop a profit from the marketing of the services has been declared by many supreme courts in various states to be a violation of the laws regulating the practice of medicine. Moreover, what is to prevent the hospital, once it has established its right to market the services of anesthesiologists, pathologists, and radiologists, to market the services of internists, surgeons, dermatologists, neurologists, or other medical specialists? For several years now most physicians have been inclined to believe that neither patients nor physicians would be any more protected by a system of marketing medical services by hospitals or other corporations than they would be if their services were marketed by governmental agencies.

Most preposterous of all is the conclusion in the editorial cited to the effect that competent physicians and specialists do not need economic protection by their special societies or by the American Medical Association. All they have to do, says the writer of this claptrap, is to put their complete confidence in their own competence and they will get all the rewards and all the protection that are coming to them. Any physician who believes that will also believe that there are good fairies and protecting angels constantly hovering at his feet and flying over his shoulders to make certain that everybody treats him with kindness and understanding in this wonderful, unselfish, and grateful world!

MORRIS FISHBEIN

DIANETICS OR THE "POOR MAN'S PSYCHOANALYSIS"

L RON HUBBARD, an engineer, explorer and writer of science fiction, is the author of a book called "Dianetics" with a subtitle "The Modern Science of Mental Health." The book is introduced by Dr. J. A. Winter, a physician, recently announced as director of the Chicago office of the Hubbard Dianetics Research Foundation. Reports indicate that the "foundation" has taken over an entire office building floor of some 18 consulting rooms in Elizabeth, New Jersey. Dr. Frederick Wertham has said that "Dianetics" is neither a good book nor a hoax but a harmful mixture of science and science fiction. The *Journal* of the American Medical Association obtained opinions from two psychiatrists who agreed that the concept is unscientific, unsupported and confusing.

The author of dianetics claims that his method has been used in a series of 270 unselected cases, including arthritis, ulcers, migraine, allergies, asthma, psychosomatic coronary difficulties *(sic)*, tendonitis, bursitis, paralysis (hysterical), eye trouble (nonpathologic) without a failure in any cases. According to Hubbard's system, psychologic difficulties are caused by "blocked engrams." The "engram" is said to be "a moment of 'unconsciousness' containing physical pain or painful emotion and all perceptions and is not available to the analytic mind as experience." Again, an "engram" is a "definite and permanent trace left by a stimulus on the protoplasm of a tissue." This assumption leads to the statement that every cell in the body has memories and these include memories derived from ancestors and others and developed in the womb, all of which memories mark the entire life of the unfortunate individual whose body is composed of these talented cells.

The writer of this weird volume suffers apparently from a *cacoethes scribendi*. Some of his paragraphs are lush outpourings of exuberant diction funnier than anything attempted in the verbal caricatures that distinguished Robert Benchley. Mr. Hubbard is so concerned about the effects of engrams that he demands that all operative procedures whether or not done under anesthesia be conducted in complete silence. Anything said during coitus, he claims, creates engrams for mother and fetus. Attempted abortions that fail create engrams

that show up in the life of the fetus many years later.

As nearly as I can make out therapy in dianetics consists of unblocking or releasing the engram. The therapist is called an auditor. As with psychoanalysis the patient is at ease. If you are an auditor you put him in reverie. Then you "install a canceller." Try to make him remember a prenatal. Ultimately you will get at a basic-basic. "You are looking for a painful, emotional engram, an instant of loss which will discharge." The discussion proceeds including mention of pre-clears, somatic strips, valence shifts, and other jargon, perhaps even beyond some of the individualistic nomenclature of advanced Freudians. The similarities to psychoanalysis are obvious. A "clear" is a person without any engrams, just as if he had been analyzed and was free from inhibitions.

The United States is overwhelmed with mind-healing cults. A new one like "dianetics" simply adds to the fun and fury. Some analysts have not been beyond retracing the infant's mental characteristics to his prenatal life. The concept of trauma on the infant's mind by attempted abortion, is, as far as I know, original with Engineer Hubbard.

Dr. J. A. Winter will no doubt open an office for treatment by the "dianetic" scheme in Chicago. Los Angeles would be better, but perhaps that gold-mine has already been assigned to some other prospector. Sooner or later some official agency will have to give this method a name—either the practice of medicine, mind-healing, or some other classification covered by the laws of the individual states. Meanwhile, dianetics is good stuff for resort conversation; perhaps by next summer something even more comical will come along.

MORRIS FISHBEIN

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The Medical Bookman

► ANGINA PECTORIS AND MYOCARDIAL INFARCTION; With Special Reference to the Autonomic Nervous System - - -

By Heymen R. Miller, M.D., Formerly Principal Physician and Chief, Signal Corps Climatic Research; Attending Physician, Sydenham Hospital; Assistant Professor of Medicine, New York Post-Graduate Medical School and Hospital; Associate Attending Physician, Montefiore Hospital. 336 pages, with 63 figures. 1950, Grune & Stratton, Inc., New York. $8.75.

Though the clinical picture of acute myocardial infarction has been recognized for over half a century and became popularly accepted after 1912 (in which year Herrick wrote the first of his classical reports), many of the problems which originally perplexed investigators of the coronary circulation are still unsolved. As listed by the author these are: "confusion arising in the concept and use of the terms anginal pain, angina pectoris, and acute myocardial infarction with or without acute coronary occlusion; lack of knowledge of the physiology of pain in general and of anginal pain in particular; the comparatively large number of unrevealed or only partially explored pathways for the transmission of anginal pain; almost total ignorance of the genesis and mechanics of emotional elements which belong with the disorders in question; and, above all, failure to appreciate that central and peripheral autonomic reactions underlie the clinical features associated with angina pectoris and acute myocardial infarction, and with acute extracardiac conditions which simulate these disorders."

The present volume, a revision and enlargement of the monograph which first appeared in 1939, represents a comprehensive examination of the present state of our knowledge of the answers to these problems. The first section on general clinical aspects of angina pectoris (acute coronary insufficiency) and acute myocardial infarction serves to refresh the reader's mind and clarify his thinking about the many clinical variations in the picture of coronary disease. Nine chapters are devoted almost exclusively to the consideration of concepts of anginal pain: pathways, reference, distribution, simulation, and mechanisms. An excellent section is devoted to psychosomatic disorders of the heart; two sound chapters to the treatment of angina pectoris and myocardial infarction. More than 40 unusually lucid illustrations show three-dimensional representations of the innervation of the heart and of nervous pathways associated with the transmission and reference of cardiac pain. These are one of the highlights of this scholarly monograph.

E. B. C.

► OFFICE TREATMENT OF THE NOSE, THROAT AND EAR - - -

By Abraham R. Hollender, M.Sc., M.D., F.A.C.S., Professor of Otolaryngology, Emeritus, University of Illinois College of Medicine; Attending Otolaryngologist, St. Francis Hospital and Mt. Sinai Hospital, Miami Beach; Consulting Otolaryngologist, Variety Children's Hospital, Miami, Florida. Ed. 3. 620 pages, illustrated. 1950, The Year Book Publishers, Inc., Chicago. $7.50.

The author rightfully calls attention to the fact that otorhinolaryngology which began and continued as a surgical specialty for many years has changed markedly since the antibiotics and other agents have come into general use. Radical operations on the nasal sinuses, for example, have been greatly reduced in number, and even acute mastoiditis is often cured now without surgical interference. However, herein lies the danger that too great dependence may be placed on the "newer remedies," and too great delay may result in emergency surgery with danger to life.

Unless prolonged rest in bed is imperative, many minor surgical operations on the ear, nose, and throat can be performed in an office sufficiently equipped to do minor surgery.

It is interesting to find a chapter devoted to "Nutritional Therapy" in which deficiency conditions related to ENT symptoms are discussed and the proper vitamins are recommended. There is also a chapter on the Psychosomatic Approach to Otolaryngology.

I. W. V.

► DISEASES OF THE HEART - - -

Diseases of the Heart. By Charles K. Friedberg, M.D., Associate Physician, Mt. Sinai Hospital, New York; Lecturer in Medicine, Columbia University. 1,081 pages, with 79 figures. 1949, W. B. Saunders Company, Philadelphia & London. $11.50.

The student and the clinician will recognize the great merit in this work by virture of the primary emphasis being placed in the pathologic physiology of cardiac disorders. Another important feature that makes this especially appealing as a text in cardiology, is the great emphasis placed on the mechanism of the symptoms and physical signs. The author presents the pathogenesis of the individual manifestations in the various cardiac diseases of circulatory failure, angina pectoris, myocardial infarction, etc.

Such an approach makes this text more than just another book on heart disease—it is a sincere attempt to teach diagnostic and therapeutic cardiology through the basic understanding of the dynamic events responsible for the clinical phenomena.

The various clinical states are dealt with individually and masterfully. With equal devotion to the ideals of pedagogy, the author presents the coronary circulation, beginning with the anatomy, followed by varieties of coronary artery disease, the arteriosclerotic heart diseases, angina pectoris and finally, acute coronary occlusion, with myocardial infarction. Thus, rheumatic fever, rheumatic heart disease, bacterial endocarditis, hypertension and renal disease and pulmonary heart disease are all discussed equally extensively with the same concise manner of approach.

Congenital heart disease is amply reviewed, covering all of the most recent advances in the field. Special emphasis is given to catheterization, oxygen and pressure studies and angiocardiography and to surgical aspects of heart disorder.

Other clinical heart diseases amenable to therapy are adequately covered, such as thyrocardiac disease, specific cardiac infections, the heart in anemia, in myxedema, in avitaminosis, and in various endocrine metabolic and nutritional disturbances. Cardiac changes in relation to the pituitary, adrenal, parathyroid, genital, thymus and pancreatic glands are presented in greater detail than generally found in standard texts. In addition, hemachromatosis, Van Gierkes disease, xanthomatosis, amyloidosis and acute porphyria are discussed. Finally, special problems in heart disease, as found in pregnancy, are well covered, as well as surgical procedures, anesthetics of choice, and medicolegal problems.

R. W.

► A GUIDE TO GENERAL MEDICAL PRACTICE - - -

By Martin G. Vorhaus, M.D., Attending Physician, Hospital for Joint Diseases, New York City. 244 pages. 1950, The Macmillan Company, New York. $3.50.

Establishing and conducting a general medical practice has always appeared formidable to those about to embark on such a venture. This volume has been written with the purpose of presenting in practical, detailed form the answers to the myriad of questions plaguing the novice.

Initially the author considers the changes and trends in medical practice during the past half-century, delineating the movement from general practice to specialization and the more recent trend back to the practice of general medicine. Factors in selecting internships, residencies, and the location of practice are set forth. The actual physical setup of the first office is discussed with an excellent section on fluoroscopic facilities. The young physician is instructed in his attitudes toward, and his dealings with, the medical and nonmedical public regarding making contacts, hospital affiliations, covering for other doctors, "stealing patients," methods of meeting competition, fees, keeping books and records, etc.

Part II explains in logical sequence the steps the physician should take in gaining the patient's cooperation, arriving at a diagnosis, and planning treatment. Complete chapters deal with the problems of various diseases, and the psychotherapy of anxiety states.

Part II discusses the important role of the physician as the adviser in family problems. The chapters are presented in lifetime chronologic sequence starting with adolescent tensions, and continuing through vocational opportunities, premarital education, sexual activity, parent-child relationships, the menopause, finally concluding with problems of the chronically ill and aged.

N. S.

► SEX QUESTIONS AND ANSWERS; A Guide to Happy Marriage - - -

By Fred Brown, Ph D., Clinical Psychologist, The Mount Sinai Hospital; Adjunct Professor of Psychology, New York University, and Rudolph T. Kempton, Ph.D., Chairman, Department of Zoology, Vassar College. Foreword by Abraham Stone, M.D. 264 pages. 1950, Whittlesey House, McGraw-Hill Book Company, Inc., Philadelphia, Toronto & London. $2.95.

During the war in 1945 the authors of this book were teaching at the Army's American University in Shrivenham, England. Students were given opportunity in an open forum to ask questions on sex. The success of the first meeting stimulated the establishment of a similar procedure in the American Zone in Germany and 22,000 men participated. Eleven hundred and twenty-six questions were accumulated and classified into 65 different categories. Most frequently asked were questions about birth control, orgasm and sterility. The ignorance of American young men on fundamental sex matters was amazing, but that has already been scientifically established by the Kinsey studies.

In this informative book the authors discuss every aspect of sex life and answer the questions that were asked by the men. The answers, which have been authenticated by four competent physicians, by health educators and psychiatrists, are direct and competent and instructive. This is the kind of sex book that can be approved for any intelligent reader and which every physician ought to read so that he may answer competently the innumerable questions of similar character that come to him.

M. F.

Books received will be acknowledged in this department each month. As space permits, books of principal interest to our readers will be reviewed more extensively.

Clinical Therapeutic Radiology. By U. V. Portmann, M.D. (Editor), Head of Department of Therapeutic Radiology, Cleveland Clinic Foundation; Professor of Therapeutic Radiology, Bunts Educational Institute, Cleveland, and 53 contributors. 748 pages, illustrated. 1950, Thomas Nelson & Sons, New York, Edinburgh & Toronto. $15.00.

Techniques in British Surgery. Edited by Rodney Maingot, F.R.C.S. 733 pages, with 473 illustrations. 1950, W. B. Saunders Company, Philadelphia & London. $15.00.

Gynecology. By John I. Brewer, B.S., M.D., Ph.D., Professor of Obstetrics and Gynecology, Northwestern University Medical School; Chief of Gynecology and Obstetrics, Passavant Memorial Hospital, Chicago. 437 pages, illustrated. 1950, Thomas Nelson & Sons, New York, Edinburgh & Toronto. $7.50.

Physician's Handbook. By Marcus A. Krupp, M.D., Assistant Clinical Professor of Medicine, Stanford University School of Medicine, San Francisco; Norman J. Sweet, M.D., Assistant Professor of Medicine, University of California School of Medicine, San Francisco; Ernest Jawetz, Ph.D., M.D., Associate Professor of Bacteriology and Lecturer in Medicine and Pediatrics, University of California School of Medicine, San Francisco, and Charles D. Armstrong, M.D., Clinical Instructor in Medicine, Stanford University School of Medicine. Ed. 6. 380 pages. 1950, University Medical Publishers, Palo Alto, California. $2.50.

The Rhesus Danger; Its Medical, Moral and Legal Aspects. By R. N. C. McCurdy, M.B., Ch.B., D.P.H., East Rudham, Norfolk, England. 138 pages. 1950, William Heinemann Medical Books Ltd., London.

Noses. By Harold M. Holden, M.D., D.D.S., Ph.D. 252 pages, illustrated. 1950, The World Publishing Company, Cleveland & New York. $3.50.

Plastic and Reconstructive Surgery; A Manual of Management. By Ferris Smith, M.D., F.A.C.S., Consultant in Plastic Surgery, Blodgett Memorial Hospital, Grand Rapids, Michigan. 895 pages, with 592 illustrations. 1950, W. B. Saunders Company, Philadelphia & London. $15.00.

Williams Obstetrics. By Nicholson J. Eastman, Professor of Obstetrics, Johns Hopkins University, and Obstetrician-in-Chief to the Johns Hopkins Hospital. Ed. 10. 1176 pages, with 651 illustrations, some in color. 1950, Appleton-Century-Crofts, Inc., New York. $12.50.

Inter-Allied Conferences on War Medicine 1942-1945. Convened by the Royal Society of Medicine. Honorary Editor: Major General Sir Henry Letheby Tidy, K.B.E., M.D., President, Inter-Allied Conferences; Lately Consulting Physician to the British Army. Assistant Editor: J. M. Browne Kutschbach, M.B., B.CH., D.P.H. 531 pages, illustrated. 1950, Staples Press Limited, London, New York & Toronto. $5.00.

A Textbook of Gynecology. By Arthur Hale Curtis, M.D., Emeritus Professor and Chairman of the Department of Obstetrics and Gynecology, Northwestern University Medical School; Formerly Chief of Gynecological Service, Passavant Memorial Hospital, Chicago, and John William Huffman, M.D., Associate Professor of Obstetrics and Gynecology, Northwestern University Medical School; Attending Gynecologist, Passavant Memorial Hospital, Chicago. Ed. 6. 799 pages, with 466 illustrations, chiefly by Tom Jones, including 37 in color. 1950, W. B. Saunders Company, Philadelphia & London. $10.00.

Medical Diagnosis; Applied Physical Diagnosis. Edited by Roscoe L. Pullen, M.D., F.A.C.P., Professor of Graduate Medicine, Director of the Division of Graduate Medicine, and Vice Dean of the School of Medicine, Tulane University of Louisiana; Senior Visiting Physician, Charity Hospital of Louisiana at New Orleans; Consultant in Medicine, Veterans Administration Hospital, New Orleans; Consultant to the Surgeon General, Department of the Army, Washington, D.C. Ed. 2. 1119 pages, with 601 figures, 48 in color. 1950, W. B. Saunders Company, Philadelphia & London. $12.50.

Consultation Service

This special consultation information service is offered as a regular monthly feature of *Postgraduate Medicine*. Subscribers are invited to call on this Service for answers to difficult medical problems from members of our Editorial Board and our Editorial Consultants best qualified to help. Each question will be answered by mail and those of general interest will be published each month. Address all communications to Consultation Service, *Postgraduate Medicine*, 516 Essex Building, Minneapolis 3, Minnesota.

RECESSIVE GENES AS A FACTOR IN MARRIAGE

QUESTION: Recently a young couple consulted me concerning the advisability of matrimony in their particular case. This man wishes to marry his first cousin once removed and the presence of diabetes mellitus and malignancy in the family history causes much concern.

The male partner is a known mild diabetic. The male partner's maternal uncle who is the female partner's maternal great uncle was also known to have diabetes.

A second maternal uncle of the male partner, this being the female partner's maternal great uncle, had cancer of the stomach.

Two maternal aunts of the male partner, these being maternal great aunts of the female partner, had a malignancy. One had malignancy of the breast and the other of the bone.

The couple desired the following questions answered:

(a) Is matrimony, with this family history, advisable?

(b) If this couple did marry, what would be the *specific chances* of their children, as well as the future generations, presenting diabetes and/or malignancy?

(c) What would be the *specific chances* of recessive traits showing up? (None are known to exist.)

Reference is hereby made to attached charts as drawn up for me by the couple.

M.D.—North Carolina

ANSWER: (a) This question cannot be answered precisely. There is a distinction between marriage and childbearing. Disregarding this distinction, the decision about having children is a very personal matter which must be made by the parties concerned after they have the available facts.

(b) There is good evidence that the tendency to diabetes is recessively inherited. Assuming that this is true, the male partner is homozygous. Consequently, his mother is heterozygous since she is not diabetic. Since neither of his maternal grandparents was diabetic (although they both lived through the sixth decade and hence had ample time for diabetes to develop), it seems reasonable to assume that neither of them was homozygous for the diabetic factor. It is also a reasonable assumption that at least one was heterozygous for it. Assuming that only one was heterozygous, it follows that there is one chance in eight (plus whatever the gene frequency is in the population) that the female partner carries a gene which in the homozygous condition leads to diabetes. Hence, on the average, there is about one chance in 16 that a child of theirs will be diabetic if it lives long enough. However, if a child of theirs does become diabetic, it would then be certain that the female partner is heterozygous and probabilities become one in two.

The genetics of susceptibility to cancer is not sufficiently understood to permit any opinion concerning the probabilities of transmission.

(c) The probability of both partners carrying the same recessive gene which was present in single dose in one of their common ancestors is one in eight. Hence, one out of 32 of their offspring, on the average, would be expected to be homozygous for a recessive gene which was present in single dose in their common ancestors. Actually, there is no way of knowing if there are any deleterious recessive genes in the family tree; however, there are theoretical reasons for believing at least one, and probably more, is present in each of us. Finally, there is no way, theoretical or otherwise, of predicting the effect of such genes as may be present.

TREATMENT OF AMEBIC COLITIS

QUESTION: Amebic dysentery: Patient is male, age 56, with recurrent attacks of abdominal cramps and dysentery. Onset usually after eating heavy meal. Occurrence every week or so, lasting two to three days. Complete gastrointestinal series negative. Rectal examination nonrevealing. Stool examinations (two) show: liquid stools, visible mucus, no visible blood. Positive for occult blood. Moderate number of cysts of Endamoeba coli and a few trophozoites and cysts of Endamoeba histolytica. Culture negative for typhoid group.

Should this patient be treated for amebic dysentery? If so, how? Is emetine dangerous? Should I turn him over to a specialist in internal medicine?

M.D.—California

ANSWER: The patient should be treated for amebic colitis. Emetine hydrochloride in the following doses is not dangerous:

Colitis caused by Endamoeba histolytica may be treated by the deep subcutaneous administration of 1 gr. of emetine hydrochloride twice daily for three days (a total dose of 6 gr.). This should be followed by carbarsone administered in doses of 0.25 gm. (capsules) after each meal for four days (a total dose of 3 gm.).

The feces should be examined for ova and parasites after a period of two to three weeks. If Endamoeba histolytica persists, the foregoing medications should be repeated.

RECURRENT LESIONS OF ORAL MUCOSA

QUESTION: A 30-year-old, apparently healthy woman has had recurrent ulcerations of the mucous membrane of the mouth for several years. Recently they have become multiple, looking like typical canker sores.

She has had no severe illness during her life and appears to be very healthy. She has no gastrointestinal symptoms, and has not had any liver disease.

She had a temperature of 99.4°F. when first seen; white blood count was 10,700. Differential not done. There is no lymphadenopathy; tongue appeared normal and teeth are in good repair.

The following therapy has given only temporary and very unsatisfactory relief: (1) hot salt water flushes; (2) hydrogen peroxide mouth wash; (3) penicillin troches; (4) aqueous gentian violet; (5) alum applications; (6) Becotin with C three times daily; (7) recently aureomycin troches gave immediate relief but the lesions recurred one week later and aureomycin is of no help now.

Her temperature now is 99.2°F.; white blood count 6,700; sedimentation rate and differential have not been received from laboratory.

Her genitourinary history is negative; she did have a scanty period last time with moderate pain.

I would appreciate any recent information that you could give me as to the etiology of this condition. I have started the patient on local application of Pyribenzamine to see if this would give any aid.

M.D.—Wisconsin

ANSWER: The problem of recurrent aphthae of the oral mucosa often torments patients and haunts the physician and dentist. Assuming that the ulcerations in your patient represent herpetic lesions of the mouth, and there is good reason to make such an assumption, there are two remaining methods of therapy.

Antibiotic therapy has offered dramatic results in some instances. Aureomycin is the drug of choice, but I have no faith in the troches for this condition. If the prior use of troches has not altered the susceptibility of the virus, the best course is 250 mg. of aureomycin by mouth every three hours or 48 hours.

If antibiotic therapy does not produce results, smallpox vaccine may be used, but not as a simple "vaccination." The course of treatment runs for five weeks. The first week ½ the contents of a capillary smallpox vaccine tube with 0.5 cc. of normal saline is injected intradermally. The second week 1 tube is used, the third week 2 tubes, the fourth week 3 tubes and the fifth week 4 tubes.

For local relief equal parts of phenol and camphor may be applied to each lesion carefully after thoroughly drying the surface.

Differential diagnosis includes pemphigus (bullous eruptions), herpes zoster (usually unilateral), erythema multiforme (usually self-limiting) and periadenitis mucosa necrotica recurrens (not preceded by vesicle). Careful observation of herpetic stomatitis will usually reveal small vesicles which rupture in an extremely short time leaving gray centered, flat, shallow ulcers with narrow red areolae. The individual lesions heal in about two weeks. The virus which appears to cause this disease is that of herpes simplex which also is the cause of herpetic lesions (cold sores) on the lips and herpetic gingivo-stomatitis in children.

HAMILTON B. G. ROBINSON, D.D.S.

HAZARDS OF HIGH ALTITUDES TO CARDIAC PATIENT

QUESTION: What are the hazards of a cardiac patient in high altitudes—say 5,000 to 10,000 feet above sea level—traveling by automobile? And what are the comments on use of Blue Capsules (methylene blue) at such altitudes? I have a patient 70 years of age who has had at least one coronary thrombosis. While he is up and at work, he does experience shortness of breath and rapid pulse. He saw something of methylene blue for these conditions. I know nothing of these blue capsules.

M.D.—Louisiana

ANSWER: To answer the above question intelligently it is necessary to have much more information than has been submitted. It is necessary to know how much damage has been done to the 70-year-old patient as a result of his coronary occlusion. What is his blood pressure? How much cardiac reserve does he have? What is his vital capacity? Does he have emphysema? The fact that he experiences shortness of breath and rapid pulse while at work would be significant of some cardiac weakness or cardiac insufficiency. Going to an altitude of 5,000 feet should not increase this very much provided he doesn't take much exercise. At 10,000 feet the available oxygen content of the air would be less, so there would be a greater tendency to anoxemia than at sea level. But even this would not be very much if the patient remained quiet and took very little or no exercise.

In regard to the use of capsules of methylene blue, I have no information concerning these and their effect on the coronary circulation.

JAMES E. PAULLIN

TREATMENT OF GIARDIASIS

QUESTION: What is the best medicine for treatment of giardiasis? The only cases I had seen prior to now were in Belgium during the war. Atabrine was found to be fairly efficacious. Is there anything better?

M.D.—California

ANSWER: Some time ago Dr. Bacigalupo, of Buenos Aires, Argentina, gave a lecture at the meeting of the Pan-American Medical Association in Havana, Cuba on the complete effectiveness of atabrine in freeing a patient of giardiasis. No failures in freeing patients of infection with Giardia lamblia have been encountered in the use of 1 tablet of atabrine (dihydrochloride—brand of quinacrine hydrochloride), 0.1 gm. being taken three times a day just before meals, for fifteen doses.

New Drugs *and* Instruments

Information published in this department has been supplied by the manufacturers of the products described.

EMERGENCY SUTURE KIT WITH ATRAUMATIC® NEEDLES ATTACHED

DESCRIPTION: Needles used are D & G atraumatic needles, particularly adaptable for emergency work and suitable for suturing skin, muscle, and tendon. A single strand of suture is swaged to the needle by means of a long flange. Suture materials are of smaller sizes: products selected are Anacap® Surgical Silk (black braided), Dermalon® (blue monofilament nylon) and mild chromic surgical gut (catgut), an absorbable suture for deeper layers.

Sutures in the kit are heat sterilized and hermetically sealed in glass tubes, the exteriors of which may be sterilized by boiling or autoclaving or submersion in any active germicidal solution.

PRODUCER: Davis & Geck, Inc., Brooklyn, N. Y.

LACRIL

PURPOSE: Artificial tears.

COMPOSITION: Isotonic solution of methyl-cellulose and sodium chloride, with methyl-paraben as a preservative. Odorless, colorless and practically tasteless, it has the approximate tonicity and viscosity of tears.

INDICATIONS FOR USE: To provide a moist surface to the cornea in the absence of normal lacrimal secretion.

DOSAGE AND ADMINISTRATION: Three or four drops in the eye, as directed by the physician.

HOW SUPPLIED: In 1-fluid ounce bottles with dropper.

PRODUCER: Abbott Laboratories, North Chicago, Ill.

BENAT WITH B_{12} (INJECTABLE)

PURPOSE: Treatment of pernicious anemia and other hyperchromic, macrocytic anemias, sprue, and other vitamin B deficiency states.

COMPOSITION: Each cubic centimeter contains:

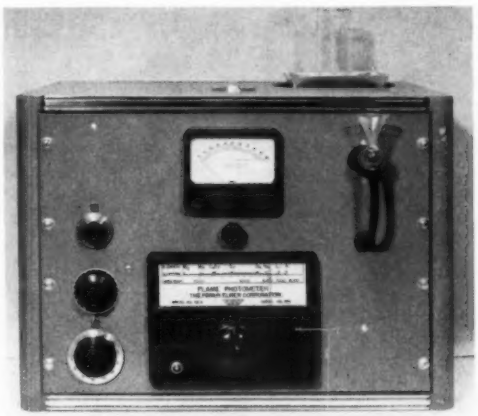
Injectable liver (crude)*	0.5 cc.
Vitamin B_{12} crystalline	10 micrograms
Niacinamide	50 mg.
Thiamine hydrochloride	10 mg.
Riboflavin	2 mg.
Pyridoxine hydrochloride	1 mg.
d-Pantothenyl alcohol	1 mg.
Benzyl alcohol	4 per cent
Phenol	0.5 per cent

DOSAGE AND ADMINISTRATION: In pernicious anemia, therapeutic—1 or 2 cc. once or twice weekly, deep intramuscularly; maintenance—1 cc. weekly. In sprue, cirrhosis, multiple vitamin B deficiencies, 5 to 10 cc. in divided doses, as indicated.

HOW SUPPLIED: In 10 cc. Injectosols.

PRODUCER: The National Drug Company, Philadelphia, Pennsylvania.

*Each cubic centimeter of injectable liver (crude) represents 2 U.S.P. units (injectable).



FLAME PHOTOMETER

PURPOSE: For base ion analysis on body fluids.

DESCRIPTION: Method (for obtaining determinations of certain alkali metals in solution) is based on same principle as classical flame test for sodium: an atomized solution is burned in a flame and the presence of elements having a characteristic flame color is detected by means of a phototube. Concentration of each element is determined by intensity of its flame color. By making simple dilutions, base ion determinations may be made of blood sera, urine and other body fluids. Substances such as food, tissue and excreta need only be placed in solution for analysis.

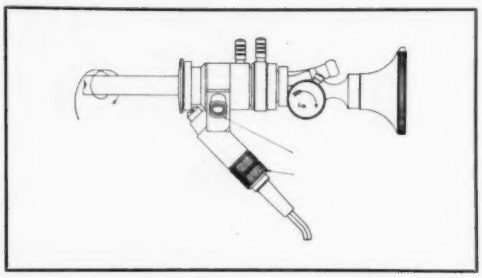
Complete details may be obtained from:

PRODUCER: The Perkin-Elmer Corp., Glenbrook, Conn.

FROST FREE REFRIGERATOR WITH BIOLOGICAL INSERTS

DESCRIPTION: Fully automatic 9.6 cubic foot refrigerator for storage of sera, blood plasma, toxins, antitoxins, and other pharmaceutical supplies in cold, dry temperatures. Features patented Frost Free system which automatically removes all frost from the freezer walls before it can build up and then disposes of the defrost water by quick evaporation outside the storage compartment. The 8-drawer biological insert is chrome steel; drawers have perforated cane sides and bottom and solid backs. Other features include a Westinghouse Sterilamp to eliminate airborne bacteria, full-width freeze chest which holds 41 pounds, storage space for 28 quarts of milk or tall bottles on top shelf, and automatic door closer.

PRODUCER: Westinghouse Electric Appliance Division, Household Refrigeration Dept., Mansfield, Ohio.



#22 FR. NATIONAL CYSTOSCOPE

DESCRIPTION: Features include: Fontar* lens system for sharper, clearer vision; both right angle and forward oblique vision; round-the-clock rotation without tangling of irrigating tube or light cord; nylon lamp capsule, no factory replacement; takes 2-6 Fr., 1-10 Fr. catheter or 11 Fr. operating instruments with telescope removable—otherwise, 2-7 Fr. or 1-11 Fr. catheter; stopcocks are removable for autoclaving.
PRODUCER: National Electric Instrument Co., Inc., Elmhurst, N. Y.
*Trademark.

POYAMIN DROPS

PURPOSE: Oral vitamin B_{12} therapy.
COMPOSITION: Each 10 cc. dropper bottle contains pure crystalline vitamin B_{12} and has been standardized to contain approximately 1 microgram of vitamin B_{12} per drop.
DOSAGE AND ADMINISTRATION: 1 to 5 drops daily or as directed by the physician. May be administered by dropping on the tongue or mixing with water, milk, fruit juice or other foods.
PRODUCER: Testagar & Co., Inc., Detroit, Mich.

FLUAGEL COMPOUND TABLETS

PURPOSE: Antacid therapy.
COMPOSITION: Combination of aluminum hydroxide gel and magnesium trisilicate, orange-flavored tablets.
DESCRIPTION: Combines with or buffers excess acid in the stomach, and provides a gelatinous film to adhere to the mucosa and, as in peptic ulcer, to intervene against the corrosive gastric juice.
HOW SUPPLIED: Bottles of 100, 500, and 1,000 tablets.
PRODUCER: George A. Breon & Co., Kansas City, Mo.

WHITE'S DIENESTROL TABLETS

PURPOSE: For use in palliative management of inoperable cancer of the prostate and the female breast; treatment of habitual and threatened abortion, and control of functional uterine bleeding.
COMPOSITION: 10 mg. scored tablets, nonsteroid, synthetic estrogen.
CAUTION: Contraindications are similar to those for any estrogen used for high-potency therapy.
HOW SUPPLIED: Bottles of 100.
PRODUCER: White Laboratories, Inc., Newark, N. J.

NEO-SYNEPHRINE HYDROCHLORIDE 0.2%

PURPOSE: Vasoconstrictor and pressor for injection.
COMPOSITION: Each 1 cc. contains 2 mg. Neo-synephrine hydrochloride.
INDICATIONS FOR USE: Stops paroxysmal tachycardia by restoring normal sinus rhythm. Also raises blood pressure in shock and shock-like states. Maintains normal blood pressure during spinal anesthesia, inhalation anesthesia (including cyclopropane) and rectal anesthesia.
DOSAGE AND ADMINISTRATION: For paroxysmal tachycardia administered by rapid intravenous injection (20 to 30 seconds), the initial dose should not exceed 0.5 mg. and not more than 1 mg. is usually necessary to produce reversion to normal rhythm. Administered subcutaneously or intramuscularly for other indications in doses of 1 to 10 mg.
HOW SUPPLIED: Ampules of 2 cc., boxes of 10; also available for parenteral use as 1% solution, vials of 5 cc. and ampules of 1 cc. (10 mg./cc.).
PRODUCER: Winthrop-Stearns, Inc., New York, N. Y.

KAO-CELLULIN

PURPOSE: Aid in restoring normal peristaltic function in fermentative and infectious diarrheas.
COMPOSITION: Each 30 cc. (approximately 1 fluid ounce) contains:
"Electros" English colloidal kaolin, 6.0 gm. (approx. 90 gr.)
Methylcellulose, 400 cps., 0.45 gm. (approx. 7 gr.)
Methylparaben U.S.P. (0.15 per cent) and propylparaben U.S.P. (0.02 per cent) as preservatives. Contains no sugar.
DOSAGE AND ADMINISTRATION: Two tablespoonfuls every two hours until primary symptoms are under control. Thereafter, one tablespoonful three times daily until normalcy is established. Dilute or follow by water. Children, one or two teaspoonfuls, according to age.
HOW SUPPLIED: Bottles of 8 ounces.
PRODUCER: Reed & Carnrick, Jersey City, N. J.

SYNOPHYLATE*

PURPOSE: Theophylline therapy.
COMPOSITION: Combination of theophylline and sodium glycinate.
INDICATIONS FOR USE: In all conditions where theophylline compounds (aminophylline, theophylline sodium acetate, theophylline sodium salicylate) are used: bronchial asthma, either allergic or secondary to emphysema; Cheyne-Stokes respiration; as a diuretic in congestive heart failure; paroxysmal dyspnea or pulmonary edema of cardiac origin.
DOSAGE AND ADMINISTRATION: Dosage and duration of treatment must be determined by the physician in each case.
HOW SUPPLIED: Tablets Synophylate (0.33 gm—5 gr.), Syrup Synophylate (each teaspoonful contains 0.33 gm.—5 gr.), and Suppositories Synophylate (each suppository contains 0.78 gm.—12 gr.).
PRODUCER: The Central Pharmacal Company, Seymour, Ind.
*Trademark.